HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SIMTRIYO safely and effectively. See full prescribing information for SIMTRIYO.

SIMTRIYO® (centanafadine) extended-release capsules, for oral use, [controlled substance schedule pending]
Initial U.S. Approval: YYYY [initial U.S. approval pending controlled substance scheduling]

WARNING: SUICIDAL IDEATION AND BEHAVIORS IN PEDIATRIC PATIENTS AGED 6 YEARS AND OLDER; and ABUSE, MISUSE AND ADDICTION
See full prescribing information for complete boxed warning.

- ***Suicidal Ideation and Behaviors*: Higher rates of suicidal ideation and behaviors occurred in SIMTRIYO-treated patients aged 6 to 12 years with attention-deficit/hyperactivity disorder (ADHD) than in placebo-treated patients. Closely monitor all pediatric patients for suicidal ideation and behaviors. Consider stopping SIMTRIYO in patients who experience emergent suicidal ideation and behavior. (5.1)**
- ***Abuse, Misuse and Addiction*: SIMTRIYO has a potential for abuse and misuse. Abuse of central nervous system (CNS) stimulants, including SIMTRIYO, can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including SIMTRIYO, can result in overdose and death. Before prescribing SIMTRIYO, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of SIMTRIYO, and proper disposal of any unused drug. Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction (5.2, 9.2, 10).**

INDICATIONS AND USAGE

SIMTRIYO is a norepinephrine-dopamine-serotonin reuptake inhibitor and central nervous system stimulant indicated for the treatment of ADHD in adults and pediatric patients 6 years of age and older weighing at least 20 kg. (1)

Limitations of Use
The use of SIMTRIYO is not recommended in pediatric patients:
- Younger than 6 years of age because this pediatric subpopulation had a higher incidence of weight loss than pediatric patients 6 years of age and older. (8.4)
- Weighing less than 20 kg because of a lack of data for this subpopulation and the risk of weight loss. (8.4).

DOSAGE AND ADMINISTRATION

- Prior to initiating SIMTRIYO, assess (2.1):
  - Risk of abuse, misuse, and addiction (5.2)
  - For presence of cardiac disease (5.3)
  - Heart rate and blood pressure (5.4)
  - Risk for developing a manic episode (5.5)
  - Family history of tics or Tourette's syndrome and clinically evaluate patients for motor or verbal tics or Tourette's syndrome (5.10)
- *Pediatric Patients Aged* (2.2):
  - *6 to 12 years:* Recommended oral dosage is based on weight.
  - *13 to 17 years:* Recommended dosage is 280 mg orally once daily.
- *Adults*: Recommended starting dosage is 210 mg orally once daily. Dosage may be increased to maximum daily dosage of 280 mg once daily based on clinical response and tolerability. (2.2)
- Administer in the morning with or without food, at approximately the same time each day. (2.3)
- Capsules may be swallowed whole or opened and entire contents sprinkled on applesauce or yogurt, or in orange juice. (2.3)

DOSAGE FORMS AND STRENGTHS

Extended-release capsules: 140 mg, 210 mg, and 280 mg of centanafadine (3)

CONTRAINDICATIONS

- Known hypersensitivity to centanafadine or any of the excipients of SIMTRIYO (4)
- Taking or within 14 days of stopping a monoamine oxidase inhibitor (4, 7)
- Patients with pheochromocytoma or a history of pheochromocytoma (4)

WARNINGS AND PRECAUTIONS

- *Risks to Patients with Serious Cardiac Disease*: Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease. (5.3)
- *Increased Blood Pressure and Heart Rate*: Assess heart rate and blood pressure following increases in dosage, and periodically while on therapy. (5.4)
- *Psychiatric Adverse Reactions:* If new psychotic or manic symptoms occur, consider discontinuing SIMTRIYO. (5.5)
- *Hypersensitivity Reactions:* Serious hypersensitivity, including anaphylaxis and angioedema, have been reported. If a clinically significant hypersensitivity reaction occurs, immediately discontinue SIMTRIYO and initiate appropriate therapy (5.6)
- *Long-Term Suppression of Growth in Pediatric Patients*: Closely monitor height, body mass index and linear growth in pediatric patients. Consider treatment interruption in patients not growing or gaining height or weight as expected. (5.7)
- *Peripheral Vasculopathy Including Raynaud's Phenomenon*: Carefully assess for digital changes during SIMTRIYO treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy. (5.8)
- *Serotonin Syndrome*: Use of SIMTRIYO with other serotonergic drugs may cause serotonin syndrome. If occurs, discontinue SIMTRIYO and/or concomitant serotonergic drug. (4, 5.9, 7)
- *Motor and Verbal Tics and Worsening of Tourette's Syndrome*: Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue SIMTRIYO if clinically appropriate. (5.10)

ADVERSE REACTIONS

Most common adverse reactions (≥5% and greater than placebo) were (6.1):
- *Pediatric Patients Aged:*
  - *6 to 12 Years*: rash, decreased appetite
  - *13 to 17 Years*: decreased appetite, nausea, rash, headache, abdominal pain
- *Adults*: headache, decreased appetite, insomnia, nausea, dry mouth, diarrhea

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Alcohol:* Avoid consumption at the same time as, and for at least two hours after, administration of SIMTRIYO. (7)
- *CYP1A2 Substrates:* Monitor for adverse reactions. Consider dosage reduction of CYP1A2 substrate. (7)
- *CNS Stimulants:* Monitor for cardiovascular adverse reactions. If cardiovascular adverse reactions occur, consider dosage reduction of concomitant CNS stimulant, or discontinuation of SIMTRIYO and/or the concomitant CNS stimulant. (7)

USE IN SPECIFIC POPULATIONS

- *Hepatic Impairment*: Not recommended for use in patients with severe hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 7/2026

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL IDEATION AND BEHAVIORS IN PEDIATRIC PATIENTS AGED 6 YEARS AND OLDER; and ABUSE, MISUSE AND ADDICTION

Suicidal Ideation and Behaviors in Pediatric Patients 6 Years of Age and Older

In a short-term (6-week) clinical study, higher rates of suicidal ideation and behavior were reported in SIMTRIYO-treated pediatric patients with attention deficit/hyperactivity disorder (ADHD) aged 6 to 12 years than in pediatric patients treated with placebo. All pediatric patients 6 years of age or older treated with SIMTRIYO should be monitored closely for suicidal ideation and behaviors, clinical worsening, or unusual changes in behavior, especially during the initial months of therapy. Families and caregivers should be advised of the need for close observation and communication with the healthcare provider. Consider stopping SIMTRIYO in patients who experience emergent suicidal ideation and behavior *[see Warnings and Precautions (5.1)]*.

Abuse, Misuse, and Addiction

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

Before prescribing SIMTRIYO, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of SIMTRIYO, and proper disposal of any unused drug. Throughout SIMTRIYO treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction *[see Warnings and Precautions (5.2) and Drug Abuse and Dependence (9.1, 9.2)]*.

1 INDICATIONS AND USAGE

SIMTRIYO is indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults and pediatric patients 6 years of age and older weighing at least 20 kg.

Limitations of Use

The use of SIMTRIYO is not recommended in pediatric patients:

- Younger than 6 years of age because this pediatric subpopulation had a higher incidence of weight loss than pediatric patients 6 years of age and older *[see Use in Specific Populations (8.4)]*.
- Weighing less than 20 kg because of a lack of data for this subpopulation and the risk of weight loss *[see Use in Specific Populations (8.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Testing and Screening Recommendations Prior to and During Treatment with SIMTRIYO

Prior to treating patients with SIMTRIYO, assess:

- The risk of abuse, misuse, and addiction *[see Warnings and Precautions (5.2)]*.
- For the presence of cardiac disease (e.g., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions (5.3)]*.

- Heart rate and blood pressure *[see Warnings and Precautions (5.4)]*.
- The risk factors for developing a manic episode (e.g., history of depressive symptoms or a family history of suicide, bipolar disorder, or depression) *[see Warnings and Precautions (5.5)]*.
- For a family history of tics or Tourette' syndrome and clinically evaluate patients for motor or verbal tics or Tourette's syndrome *[see Warnings and Precautions (5.10)]*.

2.2 Recommended Dosage

Pediatric Patients 6 Years of Age and Older Weighing at Least 20 kg

In pediatric patients 6 to 12 years of age weighing at least 20 kg, the recommended SIMTRIYO dosage is based on weight and is provided in Table 1.

Table 1: Recommended Oral Once Daily Dosage of SIMTRIYO in Pediatric Patients 6 to 12 years of Age by Body Weight

Body Weight (kg)	Dose (mg)
20 kg to less than 35 kg	140 mg
35 kg to 50 kg	210 mg
Greater than 50 kg	280 mg

In pediatric patients 13 to 17 years of age weighing at least 20 kg, the recommended SIMTRIYO dosage is 280 mg orally once daily.

The effectiveness of SIMTRIYO 140 mg once daily in patients aged 13 to 17 years and the weight-based equivalent dosage in patients aged 6 to 12 years was not established *[see Clinical Studies (14)]*. SIMTRIYO 210 mg once daily and weight-based equivalent dosages have not been studied in pediatric patients aged 6 to 17 years and are not recommended.

Adults

In adults, the recommended starting dosage of SIMTRIYO is 210 mg orally once daily. The dosage may be increased to the maximum recommended dosage of 280 mg once daily based on clinical response and tolerability.

2.3 Administration Instructions

Administer SIMTRIYO orally, in the morning, with or without food, at approximately the same time each day *[see Clinical Pharmacology (12.3)]*. Do not cut, crush, or chew the capsules.

Take SIMTRIYO capsules whole or open the capsule and sprinkle the entire contents over one tablespoon (15 mL) of applesauce or yogurt or in one tablespoon (15 mL) of orange juice. Consume immediately followed by water. Do not chew the granules. Do not save for later use.

2.4 Starting SIMTRIYO After Use of a Monoamine Oxidase Inhibitor

Must wait at least 14 days after stopping a monoamine oxidase inhibitor (MAOI) before starting SIMTRIYO *[see Contraindications (4), Warnings and Precautions (5.9), and Drug Interactions (7)]*.

2.5 Missed Doses

If a dose of SIMTRIYO is missed, administer the missed dose as soon as remembered but no later than 4 hours after the normal dosing time. Patients should not take more than one dose of SIMTRIYO in the same day.30

3 DOSAGE FORMS AND STRENGTHS

Extended-release capsules:

- 140 mg of centanafadine: capsules with light orange opaque cap (imprinted with “C140”) and white opaque body (imprinted with “Otsuka”)
- 210 mg of centanafadine: capsules with yellow opaque cap (imprinted with “C210”) and white opaque body (imprinted with "Otsuka”)
- 280 mg of centanafadine: capsules with powder blue opaque cap (imprinted with “C280”) and white opaque body (imprinted with “Otsuka”)

4 CONTRAINDICATIONS

SIMTRIYO is contraindicated in patients:

- With known hypersensitivity to centanafadine or any of the excipients of SIMTRIYO. Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with SIMTRIYO *[see Warnings and Precautions (5.6) and Adverse Reactions (6.1)]*.
- Taking, or within 14 days of stopping, MAOIs due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome *[see Warnings and Precautions (5.9) and Drug Interactions (7)]*.
- With pheochromocytoma or a history of pheochromocytoma. Serious reactions, including elevated blood pressure and tachyarrhythmia, have been reported in patients with pheochromocytoma or a history of pheochromocytoma who received a CNS stimulant.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Ideation and Behaviors in Pediatric Patients Aged 6 Years and Older

In a short-term (6-week) clinical study, higher rates of suicidal ideation and behaviors were reported in SIMTRIYO-treated pediatric patients aged 6 to 12 years of age with ADHD than in placebo-treated pediatric patients *[see Adverse Reactions (6.1)]*.

All pediatric patients 6 years of age and older treated with SIMTRIYO should be monitored closely for suicidal ideation and behavior, clinical worsening, or unusual changes in behavior, especially during the initial months of SIMTRIYO therapy.

Families and caregivers of pediatric patients 6 years of age and older treated with SIMTRIYO should be advised of the need to monitor patients for the emergence of suicidal ideation and behavior, and to report such symptoms immediately to a healthcare provider.

Consider changing the therapeutic regimen, including stopping SIMTRIYO, in patients who experience emergent suicidal ideation or behavior or symptoms that might be precursors to emerging suicidal ideation and behavior, especially if these symptoms are severe or abrupt in onset, or were not part of the patient’s presenting symptoms.

5.2 Abuse, Misuse, and Addiction

SIMTRIYO has a potential for abuse and misuse. The use of CNS stimulants, including SIMTRIYO, exposes individuals to the risks of abuse, which can lead to the development of a substance use disorder, including addiction *[see Drug Abuse and Dependence (9.1, 9.2)]*. Misuse and abuse of CNS

stimulants, including SIMTRIYO, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher dosage or unapproved methods of administration, such as snorting or injection.

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

5.3 Risks to Patients with Serious Cardiac Disease

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

Prior to treating patients with SIMTRIYO, assess for the presence of cardiac disease (e.g., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam). Avoid SIMTRIYO use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease.

5.4 Increased Blood Pressure and Heart Rate

CNS stimulants, including SIMTRIYO, can cause an increase in heart rate and blood pressure *[see Adverse Reactions (6.1]*. Concomitant use of SIMTRIYO with other CNS stimulants increases the risk of cardiovascular adverse reactions, including increased blood pressure and heart rate *[see Drug Interactions (7)]*.

Assess heart rate and blood pressure prior to initiating treatment with SIMTRIYO, following increases in dosage, and periodically while on therapy.

5.5 Psychiatric Adverse Reactions

Exacerbation of Pre-existing Psychosis in Patients with a Psychotic Disorder

CNS stimulants, including SIMTRIYO, may exacerbate 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, including SIMTRIYO, may induce a manic or mixed episode in patients with bipolar disorder. Prior to initiating SIMTRIYO treatment, screen patients for risk factors for developing a manic episode (e.g., history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms in Patients without a History of a Bipolar or Psychotic Disorder

CNS stimulants, including SIMTRIYO, at the recommended dosage, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania *[see Adverse Reactions (6.1)]*. 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 with 0% of placebo-treated patients. If such symptoms occur, consider discontinuing SIMTRIYO.

5.6 Hypersensitivity Reactions

Serious hypersensitivity reactions, including angioedema and anaphylaxis, requiring emergency treatment, have been reported during clinical trials with SIMTRIYO *[see Adverse Reactions (6.1)]*. If a clinically significant hypersensitivity reaction occurs, immediately initiate appropriate therapy and discontinue SIMTRIYO. SIMTRIYO is contraindicated in patients with known hypersensitivity to centanafadine or any of the excipients of SIMTRIYO.

5.7 Long-Term Suppression of Growth in Pediatric Patients

SIMTRIYO is not approved for use and is not recommended in pediatric patients less than 6 years of age or weighing less than 20 kg *[see Use in Specific Populations (8.4)]*. CNS stimulants, including SIMTRIYO, have been associated with weight loss. Long-term treatment with SIMTRIYO is associated with slowing of linear growth in pediatric patients, particularly those 6 to 12 years of age *[see Adverse Reactions (6.1)]*.

Closely monitor weight, body mass index, and linear growth in SIMTRIYO-treated pediatric patients. Consider treatment interruption in pediatric patients who are not growing or gaining height or weight as expected.

5.8 Peripheral Vasculopathy Including Raynaud’s Phenomenon

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

During SIMTRIYO treatment, carefully assess for digital changes. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for SIMTRIYO-treated patients who develop signs or symptoms of peripheral vasculopathy.

5.9 Serotonin Syndrome

Concomitant use of SIMTRIYO with other serotonergic drugs may cause serotonin syndrome, a potentially life-threatening condition with changes including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor *[see Drug Interactions (7)]*.

The concomitant use of SIMTRIYO is contraindicated in patients taking or within 14 days of stopping a MAOI, including linezolid or intravenous methylene blue *[see Contraindications (4)]*. If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking SIMTRIYO, discontinue SIMTRIYO before initiating treatment with the MAOI.

If concomitant use of SIMTRIYO with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms. Discontinue SIMTRIYO and/or concomitant serotonergic drug immediately if the above symptoms occur and initiate supportive symptomatic treatment.

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

CNS stimulants have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported.

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

5.11 Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5

The SIMTRIYO 210 mg capsule contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity *[see Contraindications (4)].*

6 ADVERSE REACTIONS

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

- Suicidal Ideation and Behaviors in Pediatric Patients Aged 6 Years and Older *[see Warnings and Precautions (5.1)]*
- Abuse, Misuse, and Addiction *[see Warnings and Precautions (5.2)]*
- Risks to Patients with Serious Cardiac Disease *[see Warnings and Precautions (5.3)]*
- Increased Blood Pressure and Heart Rate *[see Warnings and Precautions (5.4)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*
- Long-Term Suppression of Growth in Pediatric Patients *[see Warnings and Precautions (5.7)]*
- Peripheral Vasculopathy Including Raynaud's Phenomenon *[see Warnings and Precautions (5.8)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.9)]*
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

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

The safety of SIMTRIYO is based on studies in:

- Pediatric patients aged 4 to 17 years with ADHD who were exposed to one or more doses of SIMTRIYO in two 6-week randomized, double-blind, placebo-controlled studies (Studies 1 and 2) *[see Clinical Studies (14)]* and a long-term open-label study. SIMTRIYO is not approved for use in patients less than 6 years of age or weighing less than 20 kg *[see Indications and Usage (1)]*. In Studies 1 and 2, 608 pediatric patients 6 years of age and older were exposed

to SIMTRIYO. A total of 394 pediatric patients 6 years of age and older were treated with SIMTRIYO for at least 6 months, and 286 were treated for 12 months or longer.

- Adult patients aged 18 to 55 years with ADHD who were exposed to another formulation of centanafadine *[see Clinical Pharmacology (12.3)]* in two 6-week randomized, double blind, placebo-controlled studies (Studies 3 and 4) *[see Clinical Studies (14)]* and a long-term open-label study. In Studies 3 and 4, 586 adult patients were exposed to another formulation of centanafadine. A total of 422 adult patients were exposed to another formulation of centanafadine for at least six months and 221 were exposed for 12 months or longer.

The most common adverse reactions (≥5% and greater than placebo) in the double-blind clinical trials were:

- *Pediatric Patients Aged 6 to 12 Years*: rash, decreased appetite (see Table 2).
- *Pediatric Patients Aged 13 to 17 Years*: decreased appetite, nausea, rash, headache, abdominal pain (see Table 3).
- *Adults*: headache, decreased appetite, insomnia, nausea, dry mouth, diarrhea (see Table 4).

The most common adverse reactions associated with discontinuation (≥1%) in the pediatric and adult double-blind clinical trials were rash, decreased appetite, nausea, and somnolence.

Adverse Reactions in Pediatric Patients 6 Years of Age and Older

The safety data below are from pediatric patients aged 6 to 17 years in Studies 1 and 2 who received SIMTRIYO 280 mg (or weight-based equivalent) once daily *[see Clinical Studies (14)]*.

Table 2 presents adverse reactions reported in 2% or more of SIMTRIYO-treated pediatric patients aged 6 to 12 years and more frequently than placebo-treated patients in Study 1.

Table 2: Adverse Reactions in ≥2% of Pediatric Patients 6 to 12 Years of Age Treated with SIMTRIYO and Greater than Placebo in 6-Week Placebo-Controlled ADHD Study (Study 1)

	Placebo (N=153)	**SIMTRIYO High dose* (N=157)**
Rash[a]	0%	9%
Decreased appetite	3%	8%
Fatigue[b]	0%	4%
Abdominal pain[c]	2%	4%
Nausea	1%	3%
Pharyngitis streptococcal	2%	3%
Diarrhea	0%	2%
Influenza	0%	2%

*Weight-based equivalent dose (targeting adult exposures at 280 mg/day) *[see Dosage and Administration (2.2)]*
[a]Rash includes: drug eruption, macular rash, maculo-papular rash, morbilliform rash, papular rash, and other related terms
[b]Fatigue includes: lethargy
[c]Abdominal pain includes: upper abdominal pain, abdominal discomfort

Table 3 presents adverse reactions reported in 2% or more of SIMTRIYO-treated pediatric patients aged 13 to 17 years and more frequently than placebo-treated patients in Study 2.

Table 3: Adverse Reactions in ≥2% of Pediatric Patients 13 to 17 Years of Age Treated with SIMTRIYO and Greater than Placebo in 6-Week Placebo-Controlled ADHD Study (Study 2)

	Placebo (N=147)	SIMTRIYO 280 mg/day (N=151)
Decreased appetite	2%	15%
Nausea	3%	10%
Rash[a]	1%	8%
Headache[b]	6%	7%
Abdominal pain[c]	0%	5%
Somnolence[d]	3%	4%
Fatigue[e]	1%	3%
Dizziness	0%	3%
Nasopharyngitis	1%	3%
Insomnia[f]	1%	3%
Irritability	1%	3%
Dry mouth	0%	2%
Weight decreased	1%	2%

[a]Rash includes: drug eruption, macular rash, maculo-papular rash, morbilliform rash, papular rash, and other related terms.
[b]Headache includes: migraine
[c]Abdominal pain includes: abdominal discomfort, upper abdominal pain, abdominal tenderness, gastrointestinal pain; lower abdominal pain
[d]Somnolence includes: sedation
[e]Fatigue includes: lethargy
[f]Insomnia includes: initial insomnia

Adverse Reactions in Adults

The safety data below are based on pooled data from Studies 3 and 4 in adult patients with ADHD treated with another formulation of centanafadine for 6 weeks *[see Clinical Studies (14)]*.

Table 4 lists adverse reactions reported in ≥2% of adult patients treated with another formulation of centanafadine and more frequently than placebo-treated patients.

Table 4: Adverse Reactions in ≥2% of Adults Treated with Another Centanafadine Formulation and Greater than Placebo in 6-Week Placebo-Controlled ADHD Studies (Studies 3 and 4)

	Placebo (N=290)	Another Centanafadine Formulation Low Dose* (N=294)	Another Centanafadine Formulation High Dose* (N=292)
Headache[a]	7%	5%	8%
Decreased appetite	2%	5%	7%
Insomnia[b]	4%	5%	7%
Nausea	2%	2%	7%
Dry mouth	0%	3%	6%
Diarrhea	1%	2%	5%
Irritability	2%	3%	4%
Rash[c]	2%	2%	4%
Abdominal pain[d]	1%	2%	4%
Parasomnia[e]	1%	1%	3%
Tachycardia[f]	1%	1%	2%
Depressed mood[g]	0%	3%	2%
Anxiety[h]	1%	2%	2%
Upper respiratory tract infection	2%	5%	2%

*There are no expected differences in the safety of SIMTRIYO 210 mg and 280 mg once daily compared to the low and high doses of the other centanafadine formulation, respectively, for the treatment of ADHD in adults.
[a]Headache includes: cervicogenic headache, migraine with aura, migraine without aura, sinus headache, head discomfort, tension headache, migraine, and other related terms
[b]Insomnia includes: initial insomnia, middle insomnia, poor quality sleep, terminal insomnia, and other related terms.
[c]Rash includes: erythematous rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, and other related terms.
[d]Abdominal pain includes: abdominal discomfort, upper abdominal pain, lower abdominal pain, abdominal tenderness, gastrointestinal pain, and other related terms.
[e]Parasomnia includes: abnormal dreams, sleep terror, nightmare, somnambulism, and other related terms.
[f]Tachycardia includes: sinus tachycardia, supraventricular tachycardia, postural orthostatic tachycardia syndrome, increased orthostatic heart rate response, increased heart rate, and other related terms.
[g]Depressed mood includes: depressive symptom, depression, major depressive disorder, major depression, dysphoria, and other related terms.
[h]Anxiety includes: nervousness, panic attack, and other related terms.

Adverse Reactions Associated with Discontinuation

Pediatric Patients 6 to 12 Years of Age

In Study 1, 6% (10/157) of SIMTRIYO-treated patients aged 6 to 12 years discontinued due to adverse reactions versus 1% (2/153) of placebo-treated patients. The most frequently reported adverse reaction associated with discontinuation (1% or more and twice rate of placebo) was rash (2.5%).

Pediatric Patients 13 to 17 Years of Age

In Study 2, 8% (12/151) of SIMTRIYO-treated patients aged 13 to 17 years discontinued due to adverse reactions versus 0% (0/147) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) associated with discontinuation were rash (2%), decreased appetite (2%), nausea (2%), and somnolence (1%).

Adults

In Studies 3 and 4, 6% (18/292) of adult patients treated with the high dose of another formulation of centanafadine discontinued due to adverse reactions versus 5% (14/294) of patients treated with the low dose and 1% (4/290) of placebo-treated patients. The most frequently reported adverse reaction associated with discontinuation (1% or more and twice rate of placebo) was rash (2%).

Suicidal Ideation and Behavior

Pediatric Patients Aged 6 Years and Older

In the 6-week study in pediatric patients aged 6 to 12 years (Study 1), suicide attempt was reported in 0.7% (2/304) of SIMTRIYO-treated patients versus 0% in placebo (0/153). In the long-term open-label trial in pediatric patients aged 6 to 17 years, suicidal ideation was reported in 0.8% (5/620) of patients, leading to discontinuation in 0.6% (4/620).

Increases in Blood Pressure and Heart Rate

Pediatric Patients 6 to 12 Years of Age

Compared to placebo, short-term (6-week) treatment (Study 1) with SIMTRIYO in patients 6 to 12 years of age was associated with differences, ranging from +0.1 to +2.8 mmHg, in the mean absolute change from baseline systolic blood pressure (SBP) and with differences, ranging from -0.2 mmHg to +1.6 mmHg, in the mean absolute change from baseline diastolic blood pressure (DBP).

Patients enrolled in the long-term open-label study had mean absolute changes in baseline SBP ranging from +0.7 to +2.7 mmHg and in baseline DBP ranging from +0.5 to +2.8 mmHg through Week 88.

Pediatric Patients 13 to 17 Years of Age

During the 6-week trial (Study 2), the proportion of SIMTRIYO-treated patients 13 to 17 years of age who developed new-onset hypertension was 10.7% compared to 8.9% treated with placebo. Compared to placebo, short-term (6-week) treatment with SIMTRIYO in patients 13 to 17 years of age was associated with differences, ranging from +0.5 to +2.1 mmHg, in the mean absolute change from baseline SBP and with differences, ranging from +0.6 mmHg to +1.5 mmHg, in the mean absolute change from baseline DBP.

Patients enrolled in the long-term open-label study had mean absolute changes in baseline SBP ranging from +0.9 to +3.2 mmHg and in baseline DBP ranging from +1.7 to +3.1 mmHg through Week 88.

Adults

In Studies 3 and 4 in adults (18 to 55 years of age), increases in heart rate ≥20 beat per minute (bpm) in supine position at any visit occurred in 15% (44/292) of patients on the high dose of another formulation of centanafadine and 12% (34/294) on the low dose, versus 11% (32/290) on placebo. Increases in systolic blood pressure of ≥20 mmHg in supine position at any visit occurred in 9% (25/292) of patients treated with the high dose of another centanafadine formulation and 12% (36/294) of patients treated with the low dose, versus 7% (21/290) on placebo.

Psychiatric Adverse Reactions

Pediatric Patients 6 to 12 Years of Age

In Study 1, psychiatric adverse reactions occurring in <2% of SIMTRIYO-treated patients receiving the weight-based dose equivalent of 280 mg daily and greater than placebo included suicide attempt and insomnia. In a long-term open-label safety study, psychiatric adverse reactions led to discontinuation of SIMTRIYO in 2% of pediatric patients 6 to 12 years of age. Psychiatric adverse reactions leading to discontinuation included irritability, auditory hallucination, visual hallucination, major depression, altered mood, and suicidal ideation.

Pediatric Patients 13 to 17 Years of Age

In Study 2, psychiatric adverse reactions occurred in 9% of patients receiving 280 mg daily of SIMTRIYO compared with 3% of patients who received placebo. Irritability and insomnia were the most common psychiatric adverse reactions in this age group (see Table 3). Irritability occurred in 3% of patients receiving 280 mg SIMTRIYO compared with 1% of patients receiving placebo. Insomnia occurred in 3% of patients receiving 280 mg SIMTRIYO compared with 1% of patients receiving placebo. In a long-term open-label pediatric safety study, psychiatric adverse reactions led to discontinuation in 4% of pediatric patients 13 to 17 years of age. Psychiatric adverse reactions leading to discontinuation included suicidal ideation, depression, irritability, apathy, aggression, anxiety, defiant behavior, and feelings of worthlessness.

Adults

In Studies 3 and 4, psychiatric adverse reactions occurred in 16% of patients receiving the high dose of another centanafadine formulation, 14% of patients receiving the low dose, and 8% of patients receiving placebo. The most frequent psychiatric adverse reactions were insomnia, irritability, abnormal dreams, depressed mood, and anxiety (see Table 4). In a long-term open-label study in adults, 21% of patients experienced psychiatric adverse reactions. The most common psychiatric adverse reactions were insomnia (8%), anxiety (6%), and irritability (3%).

Hypersensitivity Reactions

In two other ADHD clinical trials, and one trial in an unapproved population, two adult patients reported angioedema, and one patient reported suspected anaphylactic reaction, some of these events required urgent treatment as outpatients.

Effects on Growth in Pediatric Patients 6 Years of Age and Older

Pediatric Patients 6 to 12 Years of Age

The mean baseline BMI in SIMTRIYO-treated patients 6 to 12 years of age compared to placebo was 20.4 kg/m^2 and 20.0 kg/m^2, respectively. Short-term (6-week) treatment (Study 1) with SIMTRIYO was associated with a mean change from baseline weight of -0.6 kg compared to +0.8 kg in placebo-treated patients at Week 6. The mean baseline weight z-score decreased by at least 0.5 in 0.8% of SIMTRIYO-treated patients compared to none in placebo-treated patients at Week 6. The mean baseline BMI z-score decreased by at least 0.5 in 7.3% of SIMTRIYO-treated patients compared to 3.2% of placebo-treated patients at Week 6.

In the SIMTRIYO long-term open-label study, 2.2% of patients had a change from baseline weight leading to a decrease in weight z-score by at least 1, 2.2% had a decrease in BMI z-score by at least 1, and 15.6% had a decrease in height z-score by at least 1 at Week 88.

Pediatric Patients 13 to 17 Years of Age

The mean baseline BMI in both SIMTRIYO- and placebo-treated patients 13 to 17 years of age was 24.4 kg/m^2; however, placebo-treated patients had higher mean baseline weight (69 kg vs. 67.7 kg) and height (167.7 cm vs. 166.7 cm). Short-term (6-week) treatment (Study 2) with SIMTRIYO was associated with a mean change from baseline weight of -1.2 kg compared to +0.6 kg in placebo-treated patients at Week 6. The mean baseline weight z score decreased by at least 0.5 in 2% of SIMTRIYO-treated patients compared to none in placebo-treated patients at Week 6. The mean baseline BMI z-score decreased by at least 0.5 in 4.9% of SIMTRIYO-treated patients compared to none in placebo-treated patients at Week 6. In the SIMTRIYO long-term open-label study, 4.6% of patients had a change from baseline weight leading to a decrease in weight z-score by at least 1, 4.6% had a decrease in BMI z-score by at least 1, and 1.5% had a decrease in height z-score by at least 1 at Week 88.

7 DRUG INTERACTIONS

Table 5 presents clinically significant drug interactions with SIMTRIYO.

Table 5: Clinically Significant Drug Interactions with SIMTRIYO

Monoamine Oxidase Inhibitors (MAOIs)	
Prevention or Management	Concomitant use of SIMTRIYO with MAOIs or within 14 days after discontinuing an MAOI is contraindicated *[see Dosage and Administration (2.4) and Contraindications (4)]*.
Mechanism and Clinical Effect(s)	Concomitant use of SIMTRIYO with MAOIs increases the risk of hypertensive crisis (potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure) and serotonin syndrome *[see Warnings and Precautions (5.9)]*.
Alcohol	
Prevention or Management	Avoid consumption of alcohol at the same time as, and for at least two hours after, administration of SIMTRIYO.
Mechanism and Clinical Effect(s)	Consumption of alcohol at the same time as, and for at least two hours after, administration of SIMTRIYO may result in a more rapid release of centanafadine. A more rapid release of centanafadine may increase exposure-related adverse reactions and may also reduce efficacy during the late hours of the dosing

	interval due to lower centanafadine exposures *[see Clinical Pharmacology (12.3)]*.
CYP1A2 Substrates	
Prevention or Management	When SIMTRIYO is used concomitantly with CYP1A2 substrates, monitor for adverse reactions and consider dosage reduction of the concomitantly used CYP1A2 substrate.
Mechanism and Clinical Effect(s)	Centanafadine is a moderate inhibitor of CYP1A2. Concomitant use with centanafadine increases exposure of CYP1A2 substrates *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions associated with these substrates.
CNS Stimulants	
Prevention or Management	Monitor for cardiovascular adverse reactions (e.g., increased blood pressure, increased heart rate) if SIMTRIYO is used with other CNS stimulants. If cardiovascular adverse reactions occur, consider reducing the dosage of the concomitant CNS stimulant or discontinuation of SIMTRIYO and/or the concomitant CNS stimulant.
Mechanism and Clinical Effect(s)	Concomitant use of SIMTRIYO with other CNS stimulants exerts additive pharmacological effects such as increase in blood pressure and heart rate *[see Warnings and Precautions (5.4)]*.
Serotonergic Drugs	
Prevention or Management	Monitor for symptoms of serotonin syndrome when SIMTRIYO is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, discontinue SIMTRIYO and/or concomitant serotonergic drug immediately and initiate supportive symptomatic treatment.
Mechanism and Clinical Effect	Concomitant use of SIMTRIYO with other serotonergic drugs may cause serotonin syndrome *[see Warnings and Precautions (5.9)]*.

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 SIMTRIYO, during pregnancy. Pregnant women exposed to SIMTRIYO and healthcare providers are encouraged to contact the National Pregnancy Registry for ADHD Medications at 1-866-961-2388 or visiting https://womensmentalhealth.org/research/pregnancyregistry/adhd-medications/.

Risk Summary

Available data from the clinical development program with SIMTRIYO use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. In embryo-fetal developmental studies, pregnant rats and rabbits received oral centanafadine during gestation. In rats, decreased maternal body weight and body weight gain and decreased fetal body weight were observed at exposures lower than the human exposure at the Maximum Recommended Human Dose (MRHD) of 280 mg. An increase in the incidence of fetal skeletal variations was observed at exposures approximately 4 times the human

exposure at the MRHD of 280 mg. In rabbits, centanafadine did not result in any effects on embryo-fetal survival or development at any dose. In a rat pre- and post-natal developmental study, oral administration of centanafadine during gestation and lactation resulted in decreased maternal body weight gain during gestation and a slight increase in the incidence of early postnatal pup mortality at exposures lower than the human exposure at the MRHD of 280 mg (see *Data*).

The 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 risks of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal study in rats, centanafadine was administered to females orally, once-daily, at dose levels of 10, 30, or 100 mg/kg during gestational development. Mean maternal body weight gain and/or absolute maternal body weights were decreased in the 30 and 100 mg/kg dose groups and correlated with reduced food consumption. Live fetal body weights were significantly reduced in the 30 and 100 mg/kg/day dose groups compared to controls. Treatment-related fetal abnormalities included a significant increase in the litter and fetal incidences of irregularly shaped cervical arches, incompletely ossified cervical arches, and short ribs in the 100 mg/kg dose group. The No Observed Adverse Effect Level (NOAEL) for both maternal toxicity and fetal development was 10 mg/kg/day, which is below the human exposure at the MRHD of 280 mg based on AUC.

The effects of centanafadine on pregnant female White New Zealand rabbits and development of the embryo and fetus was determined at doses of 3, 6, and 15 mg/kg/day. Mean maternal body weight gains were decreased in the 15 mg/kg/day dose group compared to controls. Centanafadine did not result in any effects on embryo-fetal survival, fetal body weights, or fetal external, visceral, or skeletal malformations or variations at any dose. The NOAEL for maternal toxicity was 6 mg/kg/day, which is below the human exposure at the MRHD of 280 mg based on AUC. The NOAEL for fetal development was 15 mg/kg/day, which is lower than the human exposure at the MRHD of 280 mg based on AUC.

Centanafadine was administered orally to pregnant rats during gestation and lactation at doses of 3, 10, or 30 mg/kg/day. Mean maternal body weight gain was decreased in the 30 mg/kg/day group during gestation and correlated with reduced food consumption. There was a slight increase in the incidence of early pup mortality in the 30 mg/kg/day group, which is lower than the human exposure at the MRHD based on AUC.

8.2 Lactation

Risk Summary

There are no data on the presence of centanafadine or its metabolite in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SIMTRIYO and any potential adverse effects on the breastfed child from SIMTRIYO or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of SIMTRIYO have been established for the treatment of ADHD in pediatric patients 6 years and older weighing at least 20 kg. Use of SIMTRIYO for this indication is based on evidence from two 6-week, randomized, double-blind, placebo-controlled studies in pediatric patients with ADHD and a long-term open-label study *[see Clinical Studies (14)]*. In short-term studies, increased rates of suicidal ideation and behaviors were reported in SIMTRIYO-treated patients 6 to 12 years of age *[see Warnings and Precautions (5.1)]*. Short- and long-term treatment with SIMTRIYO in pediatric patients 6 years of age and older was associated with increases in blood pressure and weight loss *[see Warnings and Precautions (5.4, 5.7) and Adverse Reactions (6.1)]*. Long term treatment with SIMTRIYO was associated with decreased linear growth *[see Warnings and Precautions (5.7) and Adverse Reactions (6.1)]*.

The safety and effectiveness of SIMTRIYO have not been established in pediatric patients less than 6 years of age or weighing less than 20 kg. The use of SIMTRIYO is not recommended in pediatric patients younger than 6 years of age because this pediatric subpopulation had a higher incidence of weight loss than pediatric patients 6 years of age and older. The use of SIMTRIYO is not recommended in pediatric patients weighing less than 20 kg because of a lack of data for this subpopulation and the risk of weight loss. A higher proportion of patients 4 to less than 6 years of age developed changes in mean baseline weight z-score and BMI z-score with short-term (6-week) SIMTRIYO treatment compared to pediatric patients 6 years of age and older. The mean baseline weight z-score decreased by at least 0.5 in 8.5% of SIMTRIYO-treated patients compared to none of the placebo-treated patients at Week 6. The mean baseline BMI z-score decreased by at least 0.5 in 25.5% of SIMTRIYO-treated patients compared to 4.2% of placebo-treated patients at Week 6. With short- and long-term SIMTRIYO treatment, a higher proportion of patients 4 to less than 6 years of age also developed decreases in heart rate of at least 10% leading to a measured heart rate below the first percentile for age compared to pediatric patients 6 years of age and older.

Juvenile Animal Toxicity Data

Juvenile rats were administered centanafadine at dose levels of 3, 10, and 30 mg/kg/day on post-natal day 21 through post-natal day 62. Lower body weights were observed at the 30 mg/kg/day dose and correlated with lower mean food consumption. A delay in preputial separation (which was associated with a decrease in body weight gain) and a slightly lower proportion of sperms with normal morphology were observed at 30 mg/kg/day, but there were no effects on fertility or reproductive performance. The NOAEL was 30 mg/kg/day, which is less than the human exposure at the MRHD of 280 mg based on AUC in pediatrics.

8.5 Geriatric Use

Clinical studies of SIMTRIYO did not include patients 65 years of age and older to determine if they respond differently than younger adult patients.

8.6 Hepatic Impairment

The pharmacokinetics of centanafadine was not studied in patients with severe hepatic impairment (Child-Pugh Class C) or in patients with mild hepatic impairment (Child-Pugh Class A). The exposure of centanafadine in patients with moderate hepatic impairment (Child-Pugh Class B) is similar to that in patients with normal hepatic function *[see Clinical Pharmacology (12.3)]*.

SIMTRIYO is not recommended in patients with severe hepatic impairment. The recommended dosage of SIMTRIYO in patients with mild (Child-Pugh A) or moderate hepatic impairment is the same as that for patients with normal hepatic function.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

SIMTRIYO contains centanafadine. (Controlled substance schedule to be determined after review by the Drug Enforcement Administration.)

9.2 Abuse

SIMTRIYO has a potential for abuse which can lead to the development of a substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

SIMTRIYO has a potential for misuse. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Misuse, like abuse, is often associated with higher doses and/or more frequent use of the drug, which may lead to adverse reactions similar to those seen in the context of abuse and substance use disorder.

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

Two human abuse potential studies were conducted with centanafadine, using individuals with a history of recreational use of stimulants as subjects:

- In the first study, single doses of centanafadine 400 mg or 800 mg immediate release formulation (approximately 2 and 4 times, respectively, the recommended starting dosage of SIMTRIYO in adults) produced scores on the subjective visual analog scale (VAS) for the primary measure of Drug Liking that were greater than placebo and were not statistically significantly less than scores produced by amphetamine 40 mg. Similarly, single doses of centanafadine 800 mg produced scores on Drug Liking that were greater than placebo and not statistically significantly less than the scores produced by lisdexamfetamine 150 mg. In this study, centanafadine also produced the adverse reaction of elevated mood (9 to 12%) comparable to amphetamine (7%) and lisdexamfetamine (12%).
- In the second study, single doses of centanafadine 200 mg, 400 mg or 800 mg immediate release formulation (approximately 1, 2, and 4 times, respectively, the recommended starting

dosage of SIMTRIYO in adults) produced scores on VAS Drug Liking that were greater than placebo but less than the scores produced by amphetamine 15 mg and 30 mg. In this study, centanafadine produced the adverse reaction of euphoric mood (17 to 30%) comparable to amphetamine (19 to 35%).

These human data demonstrate that centanafadine has abuse potential.

9.3 Dependence

Tolerance

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

Physical Dependence

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

Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation. However, in two phase 3 studies in which adults with ADHD received chronic administration of SIMTRIYO (200 and 400 mg total daily dose), abrupt discontinuation of the drug produced a very low degree of withdrawal symptoms that were indistinguishable from those produced by placebo. This suggests that even though SIMTRIYO is a CNS stimulant, it does not produce physical dependence.

10 OVERDOSAGE

Human Experience

There is limited clinical trial experience regarding SIMTRIYO overdosage in humans. During a premarketing clinical study with an immediate-release centanafadine formulation, vomiting, tachypnea, tachycardia, and elevations of blood pressure were observed at concentrations higher than the recommended dosage of SIMTRIYO.

Posterior reversible encephalopathy syndrome (PRES) symptoms including headache, altered mental status, hypertension, seizures, and visual disturbances including blindness have occurred in the setting of a CNS stimulant overdose. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Diagnosis of PRES should be confirmed by radiological procedure (e.g., MRI).

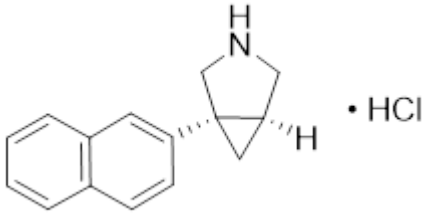
Treatment and Management

If an overdose of SIMTRIYO occurs, administer supportive care, symptomatic treatment and clinical monitoring as appropriate. Consider contacting the Poison Help Line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

SIMTRIYO is a norepinephrine-dopamine-serotonin reuptake inhibitor and central nervous system stimulant. Centanafadine hydrochloride has the chemical designation of (1*R*,5*S*)-1-(naphthalen-2-yl)-

3-azabicyclo[3.1.0]hexane hydrochloride. The molecular formula is $C_{15}H_{15}N$•HCl which corresponds to a molecular weight of 245.75 with the following structural formula:



SIMTRIYO (centanafadine) extended-release capsules for oral use contain 140 mg, 210 mg, or 280 mg of centanafadine, equivalent to 164.4 mg, 246.6 mg, or 328.8 mg, respectively, of centanafadine hydrochloride. Each capsule contains a combination of immediate release, extended release, and delayed release beads. Inactive ingredients for the beads include: colloidal silicon dioxide, ethyl acrylate and methyl methacrylate copolymer, hypromellose, mannitol, microcrystalline cellulose, plasacryl, poly (methyl acrylate-CO-methyl methacrylate-CO-methacrylic acid), polysorbate 80, and talc. The capsule shell contains: hypromellose, titanium dioxide, FD&C Blue No. 1 (280 mg capsule), FD&C Yellow No. 5 (210 mg capsule), FD&C Yellow No. 6 (140 mg capsule). The capsules are imprinted with edible black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Centanafadine has inhibitory activity at norepinephrine (NE), dopamine (DA), and serotonin (5-HT) reuptake transporters and is a central nervous system stimulant. The mechanism of action of centanafadine in the treatment of ADHD is unclear; however, its efficacy could be mediated through its activity as a norepinephrine-dopamine-serotonin reuptake inhibitor.

12.2 Pharmacodynamics

Centanafadine binds to the norepinephrine transporter, dopamine transporter, and serotonin transporter, and inhibits the reuptake of these neurotransmitters.

Cardiac Electrophysiology

At 2 times the maximum recommended dose of centanafadine, clinically significant QTc interval prolongation was not observed.

12.3 Pharmacokinetics

Following multiple doses of SIMTRIYO, peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased slightly greater than dose proportionally across the dose range of 140 to 280 mg following once-daily dosing. Steady state concentrations were achieved on Day 2 with minimal drug accumulation (1.2- to 1.3-fold).

Absorption

Time to reach C_{max} (T_{max}) of once daily SIMTRIYO extended-release capsules was 5 hours.

Effect of Food

Administration of SIMTRIYO with a high-fat meal (1000 calories, 50% fat) resulted in 29% increase in C_{max}, 1.5 hours delay in T_{max} and no change in AUC_{inf} of SIMTRIYO capsule compared to the fasted

state. The differences in pharmacokinetic parameters are not considered clinically meaningful *[see Dosage and Administration (2.3)]*.

Sprinkling the contents of a SIMTRIYO capsule on applesauce or yogurt, or in orange juice, had comparable pharmacokinetics (C_{max} and AUC) to those observed after administration of the intact capsule of SIMTRIYO *[see Dosage and Administration (2.3)]*.

Distribution

Centanafadine is highly plasma protein bound. The fraction unbound of centanafadine in the plasma of healthy adults is <0.01 and is independent of centanafadine concentrations. The apparent volume of distribution of SIMTRIYO is approximately 167 L.

Elimination

The mean half-life of SIMTRIYO is 5.2 hours. The mean apparent clearance is 410 mL/min.

Metabolism

Centanafadine is primarily metabolized by monoamine oxidase A. The lactam metabolite was the most abundant metabolite and was not pharmacologically active.

Excretion

Following administration of a ^{14}C centanafadine dose, 88% of the administered radioactivity was excreted in the urine as metabolites, and 7% was recovered in the feces.

Specific Populations

Pediatric Patients (6 to 12 years of age)

The pharmacokinetics of centanafadine (C_{max} and AUC) in pediatric patients was similar to adults following single and multiple centanafadine doses when the dosage was adjusted for weight. Similar to adults, minor accumulation was observed following multiple centanafadine doses to pediatric patients.

Patients with Renal Impairment

In adults with severe renal impairment (eGFR <30 mL/min, and not undergoing dialysis), centanafadine exposures were lower (C_{max} reduced by 25% and AUC_{inf} reduced by 20%) compared to healthy matched adults.

Patients with Hepatic Impairment

In adults with moderate hepatic impairment (Child Pugh B), centanafadine exposures were lower (C_{max} reduced by 30% and AUC_{inf} reduced by 25%) compared to healthy matched adults. The effect of severe hepatic impairment (Child Pugh C) or mild hepatic impairment (Child-Pugh Class A) on centanafadine pharmacokinetics has not been studied *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

No clinically meaningful change in pharmacokinetics of centanafadine was observed with concomitant use of ciprofloxacin (a CYP1A2 inhibitor), quinidine (a CYP2D6 inhibitor), or smoking (a CYP1A2 inducer).

Following the concomitant use of multiple oral doses of another centanafadine formulation with a caffeine citrate solution (200 mg), a CYP1A2 substrate, there was no appreciable change in the mean C_{max} of caffeine; however, there was a 2-fold increase in the AUC_{inf} of caffeine compared to a single dose administration of caffeine citrate solution (200 mg) alone *[see Drug Interactions (7)]*.

Effect of Alcohol

An *in vitro* dissolution study was conducted to evaluate the effects of alcohol on the release characteristics of centanafadine from SIMTRIYO. The study showed that 20% and 40% alcohol can cause approximately 85% and 100% of centanafadine release, respectively, within 1.5 hours compared to 23% of centanafadine release in the control (0% alcohol). At 5% alcohol, the centanafadine release was comparable to the control through 1.5 hours; however, the release was accelerated beyond that time point (i.e., after 2 hours) *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Centanafadine did not increase the incidence of tumors in rats treated for up to 91 weeks at any of the oral doses tested, up to 20 mg/kg/day in males and 30 mg/kg/day in females, which are less than the human exposure at the maximum recommended human dose (MRHD) of 280 mg based on AUC. Centanafadine did not increase the incidence of tumors in rasH2 mice treated for 26 weeks at oral doses of up to 10 mg/kg/day.

Mutagenesis

Centanafadine was not genotoxic in a battery of genotoxicity tests. Centanafadine was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay, or clastogenic in the *in vitro* mammalian chromosomal aberration assay or *in vivo* in the rat bone marrow micronucleus test.

Impairment of Fertility

Centanafadine did not impact rat fertility or reproduction at doses of 3, 10, or 30 mg/kg/day, with the highest dose tested being lower than the human exposure at the MRHD of 280 mg based on AUC.

14 CLINICAL STUDIES

Pediatric Patients with ADHD

The efficacy of SIMTRIYO for the treatment of ADHD in pediatric patients 6 years of age and older weighing at least 20 kg was evaluated in two short-term, randomized, placebo-controlled studies (Studies 1 and 2).

Study 1

Study 1 (NCT05428033) was a randomized, double-blind, multicenter, placebo-controlled study in patients 4 to 12 years of age with ADHD. SIMTRIYO is not approved for use in patients less than 6 years of age or weighing less than 20 kg *[see Indications and Usage (1)]*; efficacy results are presented only for pediatric patients 6 years of age and older.

Patients in Cohort 1 (6 to 12 years of age) were randomized 1:1:1 at baseline to receive weight-based dose equivalent to 280 mg SIMTRIYO, weight-based dose equivalent to 140 mg SIMTRIYO, or placebo once daily for 6 weeks. Patients had a mean age of 9 years (range: 6 to 12 years), 58% were male, 27% Black/African American and 65% White, and 31% were of Hispanic or Latino ethnicity.

The primary endpoint was the change from baseline at Week 6 (Day 42) in the symptoms total raw score on the ADHD Rating Scale Version 5 (ADHD-RS-5). Higher ADHD-RS-5 scores reflect more severe symptoms.

A total of 480 patients 6 to 12 years of age were randomized, 367 completed the study and 90 were discontinued. Patients treated with a weight-based dose equivalent to 280 mg SIMTRIYO once daily showed a statistically significant difference in the ADHD-RS-5 symptoms total raw score at Week 6 (Day 42) compared to patients treated with placebo (see Table 6 and Figure 1).

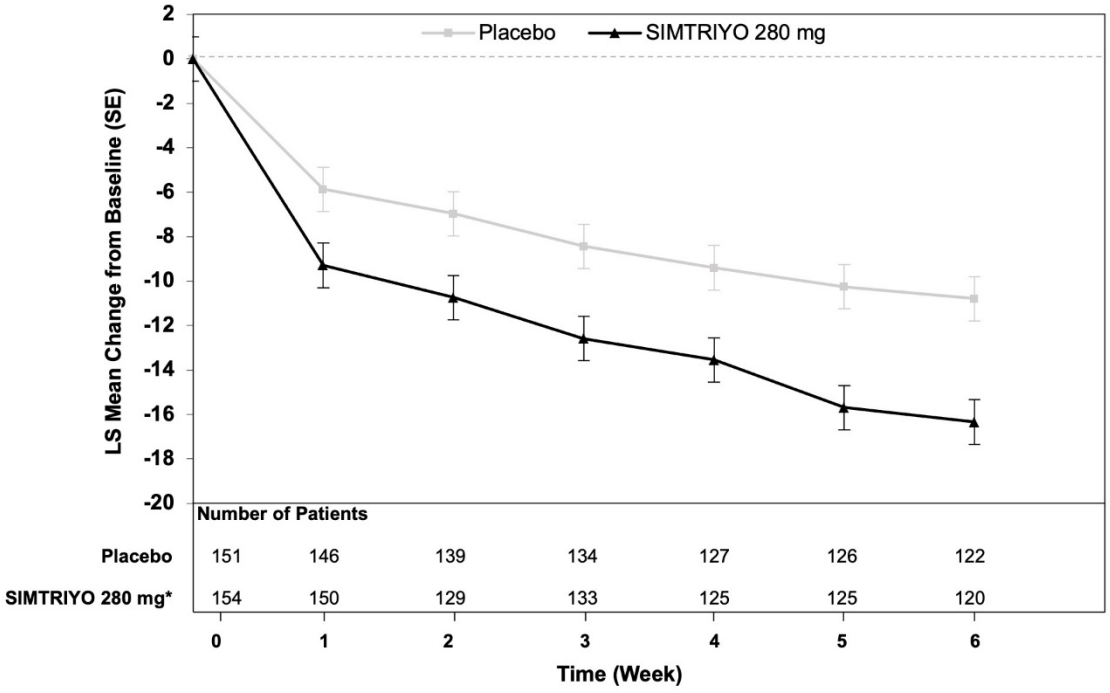
Only the weight-based dose equivalent to 280 mg SIMTRIYO once daily is approved for pediatric patients 6 to 12 years of age *[see Dosage and Administration (2.2)]*. The weight-based dose equivalent to 140 mg SIMTRIYO once daily did not demonstrate a significantly greater difference in the ADHD-RS-5 symptoms total raw score at Day 42 compared to patients treated with placebo and is not an approved dosage regimen.

Table 6: Primary Efficacy Results for Change from Baseline in ADHD-RS-5 Total Score in Pediatric Patients 6 to 12 Years of Age with ADHD (Study 1)

		Primary Efficacy Measure: ADHD-RS-5 Total Score		
Treatment Group	**N**	**Mean Baseline Score (SD)**	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference* (95% CI)**
Placebo	151	43.0 (6.69)	-10.8 (1.19)	--
SIMTRIYO 280 mg once daily†	154	43.0 (6.65)	-16.3 (1.19)	-5.6 (-8.78, -2.33)

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
*Difference (drug minus placebo) in least-squares mean change from baseline.
†Weight-based dose equivalent

Figure 1: LS Mean Change from Baseline in ADHD-RS-5 Total Score in Pediatric Patients 6 to 12 Years of Age with ADHD (Study 1)



*Weight-based dose equivalent.
LS = least squares, SE = standard error

Study 2

Study 2 (NCT05257265) was a randomized, double-blind, multicenter, placebo-controlled study in patients 13 to 17 years of age with ADHD. Patients were randomized 1:1:1 to receive 140 mg SIMTRIYO, 280 mg SIMTRIYO, or placebo once daily for 6 weeks. Patients had a mean age of 15 years (range: 13 to 17 years), 59% were male; 25% Black/African American, 70% White, and 28% were of Hispanic or Latino ethnicity.

The primary endpoint was the change from baseline at Week 6 (Day 42) in the symptoms total raw score on the ADHD Rating Scale Version 5 (ADHD-RS-5), an 18-question scale that assesses hyperactivity, impulsivity, and inattentive symptoms. Higher ADHD-RS-5 scores reflect more severe symptoms.

A total of 459 patients were randomized, 371 completed the study, and 88 were discontinued. Patients treated with 280 mg SIMTRIYO once daily showed a statistically significant difference in the ADHD-RS-5 symptoms total raw score at Week 6 (Day 42) compared to patients treated with placebo (see Table 7 and Figure 2).

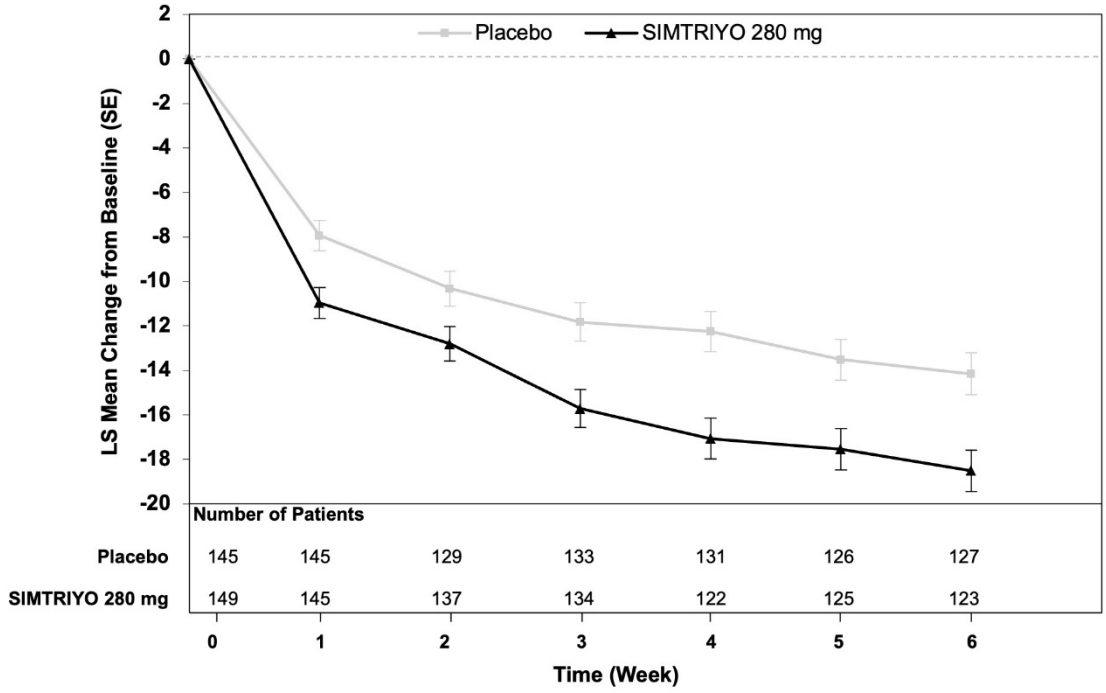
Only SIMTRIYO 280 mg once daily is approved for pediatric patients 13 to 17 years of age *[see Dosage and Administration (2.2)]*. Patients treated with 140 mg SIMTRIYO once daily did not demonstrate a significantly greater difference in the ADHD-RS-5 symptoms total raw score at Day 42 compared to patients treated with placebo and is not an approved dosage regimen.

Table 7: Primary Efficacy Results for Change from Baseline in ADHD-RS-5 Total Score in Pediatric Patients 13 to 17 Years of Age with ADHD (Study 2)

		Primary Efficacy Measure: ADHD-RS-5 Total Score		
Treatment Group	**N**	**Mean Baseline Score (SD)**	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference* (95% CI)**
Placebo	145	37.0 (5.73)	-14.2 (0.93)	--
SIMTRIYO 280 mg once daily	149	37.9 (6.46)	-18.5 (0.93)	-4.4 (-6.83, -1.87)

SD: standard deviation; SE: standard error; LS Mean: least-squares; CI: confidence interval.
*Difference (drug minus placebo) in least-squares mean change from baseline.

Figure 2: LS Mean Change from Baseline in ADHD-RS-5 Total Score in Pediatric Patients 13 to 17 Years of Age with ADHD (Study 2)



LS = least squares, SE = standard error

Adult Patients with ADHD

The efficacy of SIMTRIYO for the treatment of ADHD in adults is based on two short-term, randomized, double-blind, multicenter, placebo-controlled studies with another formulation of centanafadine (Studies 3 and 4). There are no expected differences in effectiveness of the low and high doses of the other centanafadine formulation compared to SIMTRIYO 210 mg and 280 mg once daily, respectively, for the treatment of ADHD.

In Study 3 (NCT03605680) and Study 4 (NCT03605836), patients 18 to 55 years of age were randomized (1:1:1) to receive low or high doses of another formulation of centanafadine or placebo for 6 weeks. Patients began double-blind treatment on Day 1 and continued through Day 42. Patients randomized to receive the low dose-initiated treatment on Day 1 and remained at that dose for the duration of the study. Patients randomized to receive the high dose-initiated treatment at the low dose on Day 1 through Day 7, then received the high dose on Day 8 through the duration of the study.

Study 3 included 466 patients with a mean age of 36 years (range: 18 to 55 years old); 51% were male; 14% Black/African American, 81% White, and 22% were of Hispanic or Latino ethnicity. Study 4 included 440 patients with a mean age of 35 years (range: 18 to 55 years old); 53% were male; 13% Black/African American, 79% White, and 18% were of Hispanic or Latino ethnicity.

The primary endpoint in both studies was the change from baseline at Day 42 in the ADHD Investigator Symptom Rating Scale (AISRS) total score, an 18-item scale corresponding to 18 symptoms of ADHD. Higher AISRS scores reflect more severe symptoms. The change from baseline in the Clinical Global Impression-Severity of Illness (CGI-S) score at Day 42 was the key secondary endpoint. Higher CGI-S scores reflect more severe symptoms.

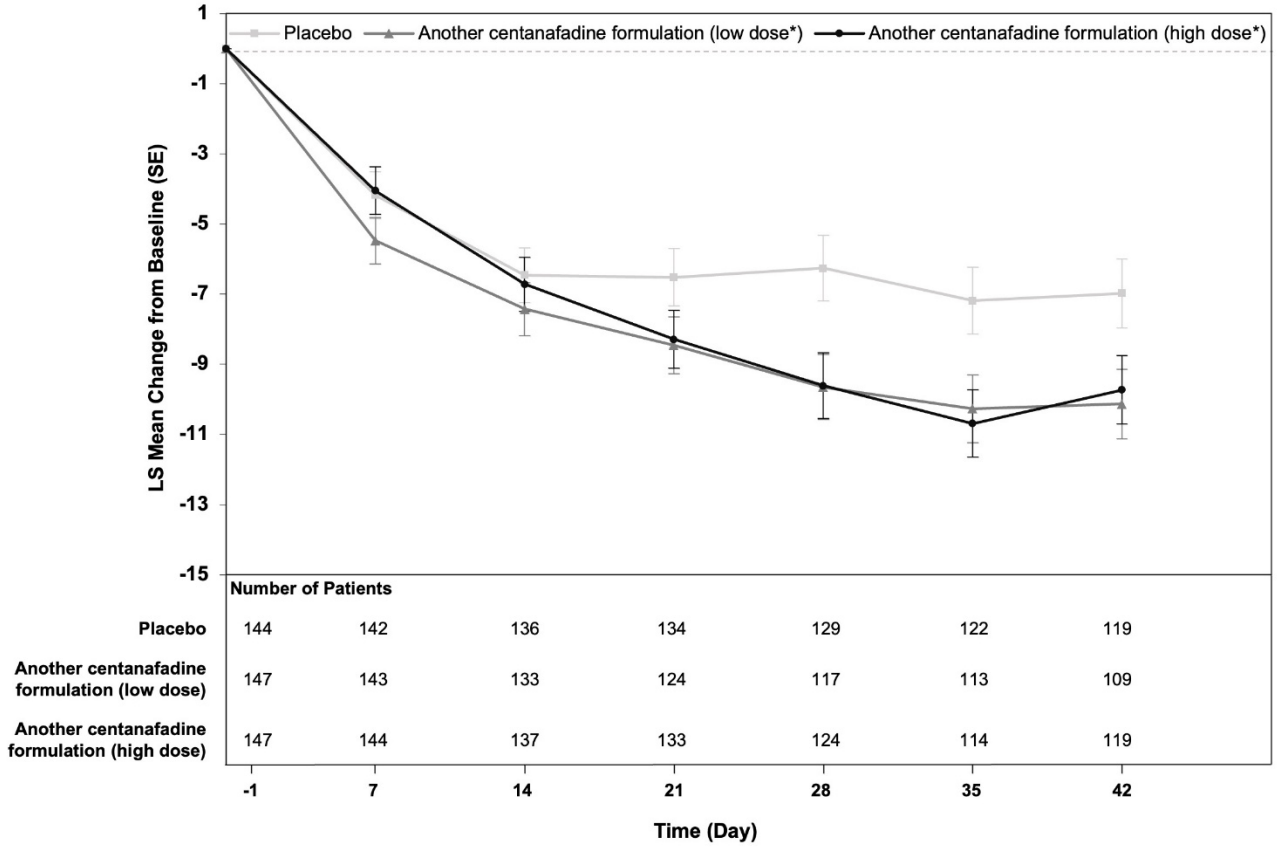
In Studies 3 and 4, a total of 906 patients were randomized; 684 completed the study, and 222 were discontinued. In both studies, the change from baseline (reduction) in the AISRS total score at Day 42 was statistically significantly greater in adults treated with another formulation of centanafadine compared to adults treated with placebo (see Table 8 and Figures 3 and 4). In addition, the change from baseline (reduction) in the CGI-S score, demonstrating reduction in the severity of symptoms of ADHD, was statistically significantly greater in adults treated with another formulation of centanafadine compared to adults treated with placebo.

Table 8: Primary Efficacy Results for Change from Baseline in AISRS Total Score in Adults with ADHD (Studies 3 and 4)

Study Number	Treatment Group	N	Primary Efficacy Measure: AISRS Total Score in Adults		
			Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
Study 3	Placebo	144	39.5 (7.20)	-7.0 (0.98)	--
	Another centanafadine formulation (low dose†)	147	39.6 (6.69)	-10.1 (0.99)	-3.2 (-5.79, -0.51)
	Another centanafadine formulation (high dose†)	147	39.6 (6.82)	-9.7 (0.98)	-2.7 (-5.35, -0.14)
Study 4	Placebo	141	37.7 (6.35)	-8.1 (0.94)	--
	Another centanafadine formulation (low dose†)	140	37.6 (6.75)	-12.1 (0.96)	-4.0 (-6.55, -1.46)
	Another centanafadine formulation (high dose†)	140	38.8 (6.96)	-12.5 (0.99)	-4.4 (-7.02, -1.82)

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
*Difference (drug minus placebo) in least-squares mean change from baseline.
†There are no expected differences in effectiveness of SIMTRIYO 210 mg and 280 mg once daily compared to the low and high doses of the other centanafadine formulation, respectively, for the treatment of ADHD in adults.

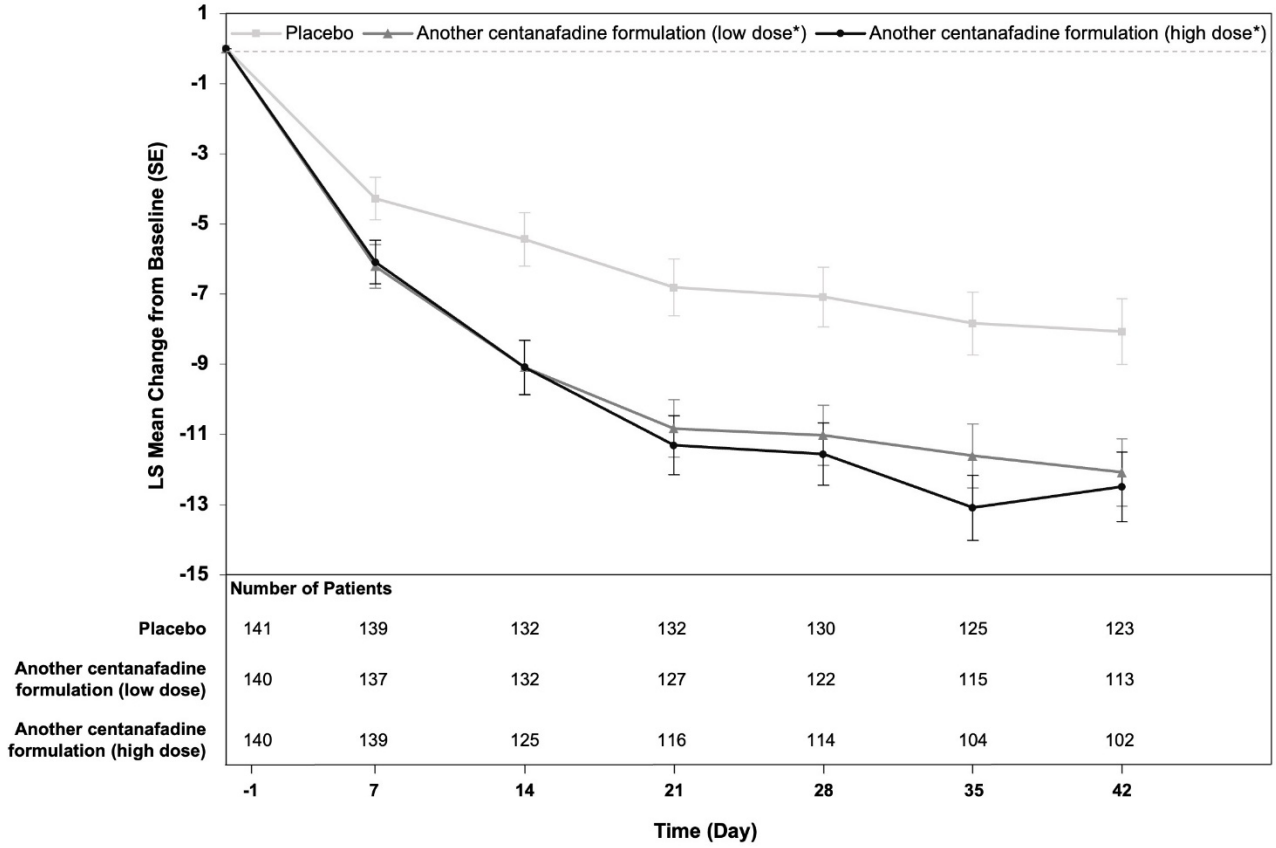
Figure 3: LS Mean Change from Baseline in AISRS Total Score in Adults with ADHD (Study 3)



LS = least squares, SE = standard error

* There are no expected differences in effectiveness of SIMTRIYO 210 mg and 280 mg once daily compared to the low and high doses of the other centanafadine formulation, respectively, for the treatment of ADHD in adults.

Figure 4: LS Mean Change from Baseline in AISRS Total Score in Adults with ADHD (Study 4)



LS = least squares, SE = standard error

* There are no expected differences in effectiveness of SIMTRIYO 210 mg and 280 mg once daily compared to the low and high doses of the other centanafadine formulation, respectively, for the treatment of ADHD in adults.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

SIMTRIYO (centanafadine) extended-release capsules are available as follows:

Strength	Colors	Imprint codes	Size	NDC
140 mg	light orange opaque cap/white opaque body	“C140” (cap) and “Otsuka” (body)	Bottle of 30	59148-302-13
210 mg	yellow opaque cap/white opaque body	“C210” (cap) and “Otsuka” (body)	Bottle of 30	59148-303-13
280 mg	powder blue opaque cap/white opaque body	“C280” (cap) and “Otsuka” (body)	Bottle of 30	59148-304-13

Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

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

Suicidal Ideation and Behaviors

Patients, their families, and their caregivers should be alerted about the need to monitor patients for the emergence of suicidal ideation and behavior, especially during the first few months of SIMTRIYO

treatment. Such symptoms should be reported to the patient's healthcare provider immediately *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Abuse, Misuse, and Addiction

Educate patients and their families about the risks of abuse, misuse, and addiction of SIMTRIYO, which can lead to overdose and death, and proper disposal of any unused drug. Advise patients to store SIMTRIYO in a safe place, preferably locked, and instruct patients to not give SIMTRIYO to anyone else *[see Warnings and Precautions (5.2), Drug Abuse and Dependence (9.1, 9.2), and Overdosage (10)]*.

Risks to Patients with Serious Cardiac Disease

Advise patients and their caregivers that there are potential risks to patients with serious cardiac disease, including sudden death, with SIMTRIYO 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 (5.3)].*

Increased Blood Pressure and Heart Rate

Advise patients and their caregivers that SIMTRIYO can cause elevations in blood pressure and heart rate *[see Warnings and Precautions (5.4)]*.

Psychiatric Adverse Reactions

Advise patients and their caregivers that SIMTRIYO, at recommended doses, may cause psychotic or manic symptoms, even in patients without a prior history of psychotic symptoms *[see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions, including anaphylaxis, angioedema and rash, have occurred with SIMTRIYO. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction *[see Warnings and Precautions (5.6)]*.

Long-term Suppression of Growth in Pediatric Patients

Advise patients, and their caregivers that SIMTRIYO may cause slowing of growth and weight loss in pediatric patients. Height and weight should be monitored while using SIMTRIYO *[see Warnings and Precautions (5.7)]*.

Peripheral Vasculopathy, Including Raynaud's Phenomenon

Instruct patients and their caregivers about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms; to report to their healthcare provider any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes; to call their healthcare provider immediately with any signs of unexplained wounds appearing on fingers or toes while taking SIMTRIYO *[see Warnings and Precautions (5.8)]*.

Serotonin Syndrome

Inform patients and their caregivers that use of SIMTRIYO with other serotonergic drugs may cause serotonin syndrome. Instruct patients who are taking other serotonergic drugs to contact their healthcare provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome *[see Warnings and Precautions (5.9) and Drug Interactions (7)]*.

Allergic Reactions and Reactions to FD&C Yellow No. 5 (Tartrazine)

Advise patients that the SIMTRIYO 210 mg capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons or in patients who also have an aspirin hypersensitivity. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction *[see Warnings and Precautions (5.11)]*.

Pregnancy

Advise patients about the pregnancy exposure registry that monitors outcomes in women exposed to ADHD medications, including SIMTRIYO, during pregnancy *[see Use in Specific Populations (8.1)].*

Administration Instructions

Instruct patients to take SIMTRIYO in the morning, with or without food, at approximately the same time each day. Advise patients to not cut, chew or crush the capsules. Instruct patients to swallow SIMTRIYO whole or open the capsule and sprinkle the contents over one tablespoon (15 mL) of applesauce or yogurt or in one tablespoon (15 mL) of orange juice. Advise patients to consume the contents immediately, without chewing the granules, and not to store for future use *[see Dosage and Administration (2.3)]*.

Effect of Alcohol

Advise patients to avoid consuming alcohol at the same time as, and for at least two hours after, taking SIMTRIYO. Inform patients that consuming alcohol at the same time as, or within two hours after, taking SIMTRIYO may result in a more rapid release of centanafadine *[see Drug Interactions (7)].*

Missed Dose Instructions

Advise patients that if a dose is missed, it should be taken as soon as remembered, but no later than 4 hours after the normal dosing time. Advise patients to not take more than one dose of SIMTRIYO in the same day *[see Dosage and Administration (2.5)]*.

Manufactured for Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

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MEDICATION GUIDE

SIMTRIYO® (Sim-TREE-YO)

(centanafadine)

extended-release capsules, for oral use, [controlled substance schedule pending]

What is the most important information I should know about SIMTRIYO?

SIMTRIYO may cause serious side effects, including:

- **Suicidal thoughts and actions in children 6 years of age and older.** Suicidal thoughts and actions can happen in children 6 years of age and older with attention deficit hyperactivity disorder (ADHD), **especially within the first few months of treatment.**

  How can I watch for and try to prevent suicidal thoughts and actions?

  - Pay close attention to and tell your healthcare provider right away about any changes, especially sudden changes in mood, behavior, actions, thoughts or feelings, or suicidal thoughts or actions. This is very important when SIMTRIYO treatment is started.
  - Keep all follow-up visits with your healthcare provider as scheduled. Tell your healthcare provider about symptoms between visits as needed, especially if you have concerns.

  Tell a healthcare provider right away if any of the following symptoms develop during treatment, especially if they are new, worse, or worry you:

  - thoughts about suicide or dying
  - suicide attempts
  - new or worsening depression
  - new or worsening anxiety
  - feeling very agitated or restless
  - panic attacks
  - trouble sleeping (insomnia)
  - new or worsening irritability
  - acting aggressive, being angry, or violent
  - acting on dangerous impulses
  - an extreme increase in activity and talking (mania)
  - other unusual changes in behavior or mood
- **Abuse, misuse, and addiction.** SIMTRIYO has a chance for abuse and misuse and may lead to substance use problems, including addiction. Misuse and abuse of SIMTRIYO can lead to overdose and death. The risk of overdose and death is increased with higher doses of SIMTRIYO or when it is used in ways that are not approved, such as snorting or injection.
  - Your healthcare provider should check you or your child's risk for abuse, misuse, and addiction before starting treatment with SIMTRIYO and will monitor you or your child during treatment.
  - Do not give SIMTRIYO to anyone else because it may cause death or harm them.
  - Keep SIMTRIYO in a safe place and properly dispose of any unused medicine. See "**How should I store SIMTRIYO?**" for more information.
  - Tell your healthcare provider if you or your child have ever abused or been dependent on alcohol, prescription medicines, or street drugs.

See **"What are the possible side effects of SIMTRIYO?"** for more information about side effects.

What is SIMTRIYO?

SIMTRIYO is a prescription medicine used to treat attention deficit hyperactivity disorder (ADHD) in adults and children 6 years of age and older weighing at least 44 pounds (20 kg).

SIMTRIYO is not recommended for use in children under 6 years of age or weighing less than 44 pounds (20 kg).

SIMTRIYO is a federally controlled substance (insert controlled substance schedule) because it contains centanafadine that can be a target for people who abuse prescription medicines or street drugs.

Who should not take SIMTRIYO?

Do not take SIMTRIYO if you or your child:

- are allergic to centanafadine or any of the ingredients in SIMTRIYO. See the end of this Medication Guide for a complete list of ingredients in SIMTRIYO.
- are taking, or have stopped taking within the past 14 days, a medicine called a monoamine oxidase inhibitor (MAOI).
- have a condition called pheochromocytoma (a rare tumor that usually grows in the adrenal glands which are above your kidneys).

Before taking SIMTRIYO, tell your healthcare provider about all your or your child's medical conditions, including if you or your child:

- have heart problems, heart disease, heart defects, or have a family history of sudden death, or high blood pressure

- have mental problems including psychosis, mania, bipolar illness, or depression, or have a family history of suicide, bipolar illness, or depression
- have circulation problems in fingers and toes
- have or had uncontrolled movements or sounds (tics) or Tourette's syndrome, or have a family history of tics or Tourette's syndrome
- have an allergy or sensitivity to FD&C Yellow No. 5 (tartrazine)
- have liver problems
- are pregnant or plan to become pregnant. It is not known if SIMTRIYO will harm the unborn baby. Talk to your healthcare provider about the risk to the unborn baby if you or your child take SIMTRIYO during pregnancy.
    - There is a pregnancy exposure registry for women who are exposed to SIMTRIYO during pregnancy. If you or your child become pregnant during treatment with SIMTRIYO, talk to your healthcare provider about registering with the National Pregnancy Registry for ADHD Medications at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/research/pregnancyregistry/adhd-medications/.
- are breastfeeding or plan to breastfeed. It is not known if SIMTRIYO passes into the breast milk. Talk to your healthcare provider about the best way to feed the baby during treatment with SIMTRIYO.

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

SIMTRIYO and certain other medicines may affect each other causing possible serious side effects.

Especially tell your healthcare provider if you or your child take:

- a MAOI, including linezolid or intravenous methylene blue
- medicines used to treat mood, anxiety, psychotic or thought disorders, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants
- medicines used to treat migraine headaches called triptans
- tramadol, fentanyl, meperidine, methadone, or other opioids
- tryptophan
- St. John's Wort
- other central nervous system (CNS) stimulants including other ADHD medicines

Ask your healthcare provider if you are not sure if you or your child take any of these medicines. Your healthcare provider can tell you if it is safe to take SIMTRIYO with other medicines.

Do not start any new medicine during treatment with SIMTRIYO without first talking to your healthcare provider.

Know the medicines you or your child takes. Keep a list of them and show it to your healthcare provider and pharmacist when you or your child get a new medicine.

How should I take SIMTRIYO?

- Take SIMTRIYO exactly as your healthcare provider tells you to take it.
- Take SIMTRIYO 1 time each day in the morning at about the same time each day.
- Take SIMTRIYO with or without food.
- **Swallow SIMTRIYO capsules whole. Do not** cut, crush, or chew the capsules.
- **If SIMTRIYO cannot be swallowed whole**:
    - Open the capsule and sprinkle the entire contents over 1 tablespoon (15 mL) of applesauce or yogurt, **or** in 1 tablespoon (15 mL) of orange juice.
    - Swallow all of the mixture right away.
    - Drink water right after swallowing the mixture.
    - **Do not** chew the granules.
    - **Do not** save the mixture for later use.
- If you or your child miss a dose of SIMTRIYO, take it as soon as you remember but no later than 4 hours after the normal dosing time. **Do not** take more than 1 dose of SIMTRIYO in the same day.
- If you or your child take too much SIMTRIYO, call your healthcare provider or Poison Help Line at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What should I avoid while taking SIMTRIYO?

Do not drink alcohol at the same time or within 2 hours of taking SIMTRIYO. This may cause a faster release of the SIMTRIYO medicine and can affect the way SIMTRIYO works and increase your risk for side effects.

What are the possible side effects of SIMTRIYO?

- See **"What is the most important information I should know about SIMTRIYO?"**
- **Risks in people with serious heart disease.** Sudden death has happened in people who have heart defects or other serious heart disease. Your healthcare provider should check you or your child carefully for heart problems before starting treatment with SIMTRIYO. Tell your healthcare provider or go to the nearest emergency room right away if any signs of heart problems develop such as chest pain, shortness of breath, or fainting.
- **Increased blood pressure and heart rate.** Your healthcare provider should check you or your child's blood pressure and heart rate before starting treatment, if the dose is increased, and as needed during treatment with SIMTRIYO.
- **Mental problems (psychiatric reactions), including:**
  - worsening behavior or thought problems in people with thought or psychotic disorders
  - manic episodes in people with bipolar disorder
  - new psychotic or manic symptoms in people without bipolar or psychotic disorders

  Tell your healthcare provider right away if any mental symptoms or problems develop or worsen during treatment with SIMTRIYO, including:
  - greatly increased energy
  - racing thoughts
  - unusually grand ideas
  - talking more or faster than usual
  - severe trouble sleeping
  - reckless behavior
  - excessive happiness or irritability
  - seeing or hearing things that are not real (hallucinations).
- **Allergic reactions, including serious allergic reactions (anaphylaxis).** Serious allergic reactions can happen during treatment with SIMTRIYO and can lead to hospitalization. Your healthcare provider may stop treatment with SIMTRIYO if you develop allergic reactions. Tell your healthcare provider right away if you get any signs or symptoms including:
  - raised, red areas on your skin (hives)
  - skin redness or rash, itching, flaking or peeling
  - dizziness or fainting
  - swelling of face, eyes, lips, throat, or other areas
  - difficulty in breathing or swallowing
- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with SIMTRIYO. SIMTRIYO treatment may be stopped if your child is not growing or gaining weight as expected.
- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud's phenomenon)**. Tell your healthcare provider if any of the following signs and symptoms of circulation problems develop during treatment:
  - fingers or toes feel numb, cool, painful
  - fingers or toes change color from pale, to blue, to red
  - sensitivity to temperature in fingers or toes

  Call your healthcare provider right away if any unexplained wounds appear on the fingers or toes during treatment with SIMTRIYO.
- **Serotonin Syndrome.** A potentially life-threatening problem called serotonin syndrome can happen when you take SIMTRIYO with certain other medicines. See **"Who should not take SIMTRIYO?"** and **"Especially tell your healthcare provider if you or your child take:"** Stop taking SIMTRIYO and tell your healthcare provider or go to the nearest hospital emergency room right away if any of the following signs and symptoms develop during treatment:
  - agitation
  - confusion
  - fast heartbeat
  - dizziness
  - flushing
  - tremors, stiff muscles, or muscle twitching
  - seizures
  - coma
  - changes in blood pressure
  - sweating
  - high body temperature (hyperthermia)
  - loss of coordination
  - nausea, vomiting, diarrhea
  - seeing or hearing things that are not real (hallucinations)
- **New or worsening tics or worsening Tourette's syndrome**. Tell your healthcare provider if any new or worsening tics or worsening Tourette's syndrome symptoms develop during treatment with SIMTRIYO.
- **Allergic reactions to FD&C Yellow No. 5.** SIMTRIYO 210 mg capsules contain a yellow food dye called tartrazine (FD&C No. 5) which may cause allergic-type reactions (including bronchial asthma) in certain people. If you are

allergic to aspirin, you may be more likely to react to tartrazine. Tell your healthcare provider if any symptoms of allergic reactions develop during treatment, including hives, rash, swelling, or trouble breathing.

The most common side effects of SIMTRIYO in children 6 to 12 years of age include:

- rash
- decreased appetite

The most common side effects of SIMTRIYO in children 13 to 17 years or age include:

- decreased appetite
- nausea
- rash
- headache
- stomach area (abdominal) pain

The most common side effects of SIMTRIYO in adults include:

- headache
- decreased appetite
- trouble sleeping (insomnia)
- nausea
- dry mouth
- diarrhea

These are not all the possible side effects of SIMTRIYO.

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 SIMTRIYO?

- Store SIMTRIYO at room temperature, between 68°F to 77°F (20°C to 25°C).
- Store SIMTRIYO in a safe place, like a locked cabinet.
- Dispose of remaining, unused, or expired SIMTRIYO by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or DEA authorized collector is available, mix SIMTRIYO 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 SIMTRIYO in the household trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Keep SIMTRIYO and all medicines out of the reach of children.

General information about the safe and effective use of SIMTRIYO.

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

What are the ingredients in SIMTRIYO?

Active ingredient: centanafadine

Inactive ingredients: The capsule beads contain colloidal silicon dioxide, ethyl acrylate and methyl methacrylate copolymer, hypromellose, mannitol, microcrystalline cellulose, plasacryl, poly (methyl acrylate-CO-methyl methacrylate-CO-methacrylic acid), polysorbate 80, and talc. The capsule shells contain hypromellose, titanium dioxide, FD&C Blue 1 (280 mg), FD&C Yellow 5 (210 mg), and FD&C Yellow 6 (140 mg). The capsules are imprinted with edible black ink.

Manufactured for Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

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For more information about SIMTRIYO go to www.simtriyo.com or call 1-833-468-7852.

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