

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TRULANCE (plecanatide) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

See full prescribing information for complete boxed warning.

- TRULANCE is contraindicated in patients less than 6 years of age; in young juvenile mice, plecanatide caused death due to dehydration. (4, 8.4)
- Avoid use of TRULANCE in patients 6 years to less than 18 years of age. (5.1, 8.4)
- The safety and effectiveness of TRULANCE have not been established in patients less than 18 years of age. (8.4)

RECENT MAJOR CHANGES

Indications and Usage (1)	01/2018
Dosage and Administration, Recommended Dosage (2.1)	01/2018
Warnings and Precautions, Diarrhea (5.2)	01/2018

INDICATIONS AND USAGE

TRULANCE is a guanylate cyclase-C agonist indicated in adults for treatment of:

- chronic idiopathic constipation (CIC). (1)
- irritable bowel syndrome with constipation (IBS-C). (1)

DOSAGE AND ADMINISTRATION

The recommended adult dosage of TRULANCE is

- CIC: 3 mg taken orally once daily. (2.1)
- IBS-C: 3 mg taken orally once daily. (2.1)

Administration Instructions (2.2):

- Take with or without food.
- Swallow tablets whole.
- For patients who have difficulty swallowing tablets whole or those with a nasogastric or gastric feeding tube, see full prescribing information with instructions for crushing the tablet and administering with applesauce or water.

DOSAGE FORMS AND STRENGTHS

Tablets: 3 mg (3)

CONTRAINDICATIONS

- Patients less than 6 years of age due to the risk of serious dehydration. (4, 5.1, 8.4)
- Patients with known or suspected mechanical gastrointestinal obstruction. (4)

WARNINGS AND PRECAUTIONS

Diarrhea: Patients may experience severe diarrhea. If severe diarrhea occurs, suspend dosing and rehydrate the patient. (5.2)

ADVERSE REACTIONS

Most common adverse reaction ($\geq 2\%$) is diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Synergy Pharmaceuticals at 1-888-869-8869 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Recommended Dosage
 - 2.2 Preparation and Administration Instructions
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Risk of Serious Dehydration in Pediatric Patients
 - 5.2 Diarrhea
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Trials Experience
- 8 USE IN SPECIFIC POPULATIONS
 - 8.1 Pregnancy
 - 8.2 Lactation
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use

- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES
 - 14.1 Chronic Idiopathic Constipation (CIC)
 - 14.2 Irritable Bowel Syndrome with Constipation (IBS-C)
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- TRULANCE is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile mice administration of a single oral dose of plecanatide caused deaths due to dehydration [see *Contraindications (4)*, *Use in Specific Populations (8.4)*].
- Avoid use of TRULANCE in patients 6 years to less than 18 years of age [see *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.4)*].
- The safety and effectiveness of TRULANCE have not been established in patients less than 18 years of age [see *Use in Specific Populations (8.4)*].

1 INDICATIONS AND USAGE

TRULANCE is indicated in adults for the treatment of:

- chronic idiopathic constipation (CIC).
- irritable bowel syndrome with constipation (IBS-C)

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of TRULANCE for the treatment of CIC and IBS-C is 3 mg taken orally once daily.

2.2 Preparation and Administration Instructions

- Take TRULANCE with or without food [see *Clinical Pharmacology (12.3)*].
- If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take two doses at the same time.
- Swallow a tablet whole for each dose.
- For adult patients with swallowing difficulties, TRULANCE tablets can be crushed and administered orally either in applesauce or with water or administered with water via a nasogastric or gastric feeding tube. Mixing TRULANCE crushed tablets in other soft foods or in other liquids has not been tested.

Oral Administration in Applesauce:

1. In a clean container, crush the TRULANCE tablet to a powder and mix with 1 teaspoonful of room temperature applesauce.
2. Consume the entire tablet-applesauce mixture immediately. Do not store the mixture for later use.

Oral Administration in Water:

1. Place the TRULANCE tablet in a clean cup.
2. Pour approximately 30 mL of room temperature water into the cup.
3. Mix by gently swirling the tablet and water mixture for at least 10 seconds. The TRULANCE tablet will fall apart in the water.
4. Swallow the entire contents of the tablet water mixture immediately.
5. If any portion of the tablet is left in the cup, add another 30 mL of water to the cup, swirl for at least 10 seconds, and swallow immediately.
6. Do not store the tablet-water mixture for later use.

Administration with Water via a Nasogastric or Gastric Feeding Tube:

1. Place the TRULANCE tablet in a clean cup with 30 mL of room temperature water.

2. Mix by gently swirling the tablet and water mixture for at least 15 seconds. The TRULANCE tablet will fall apart in the water.
3. Flush the nasogastric or gastric feeding tube with 30 mL of water using a catheter tip syringe.
4. Draw up the mixture using the syringe and immediately administer via the nasogastric or gastric feeding tube. Do not reserve for future use.
5. If any portion of the tablet is left in the cup, add another 30 mL of water to the cup, swirl for at least 15 seconds, and using the same syringe, administer via the nasogastric or gastric feeding tube.
6. Using the same or a fresh syringe, flush the nasogastric or gastric feeding tube with at least 10 mL of water.

3 DOSAGE FORMS AND STRENGTHS

TRULANCE Tablets:

3 mg: white to off-white, plain, round tablet debossed with “SP” on one side and “3” for 3 mg on the other side.

4 CONTRAINDICATIONS

TRULANCE is contraindicated in:

- Patients less than 6 years of age due to the risk of serious dehydration [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].
- Patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Dehydration in Pediatric Patients

TRULANCE is contraindicated in patients less than 6 years of age. The safety and effectiveness of TRULANCE in patients less than 18 years of age have not been established. In young juvenile mice (human age equivalent of approximately 1 month to less than 2 years), plecanatide increased fluid-secretion into the intestines as a consequence of stimulation of guanylate cyclase-C (GC-C), resulting in mortality in some mice within the first 24 hours, apparently due to dehydration. Due to increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than patients 6 years of age and older to develop severe diarrhea and its potentially serious consequences.

Avoid the use of TRULANCE in patients 6 years to less than 18 years of age. Although there were no deaths in older juvenile mice, given the deaths in younger mice and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of TRULANCE in patients 6 years to less than 18 years of age [*see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.4)*].

5.2 Diarrhea

Diarrhea was the most common adverse reaction in four placebo-controlled clinical trials, two in patients with CIC and two in patients with IBS-C. Severe diarrhea was reported in 0.6% of patients in two trials in patients with CIC and in 0.6% of patients in the two trials in patients with IBS-C [*see Adverse Reactions (6.1)*]. If severe diarrhea occurs, suspend dosing and rehydrate the patient.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Demographic characteristics were comparable between the TRULANCE and placebo groups in all studies [see *Clinical Studies (14)*].

Chronic Idiopathic Constipation (CIC)

The safety data described below reflect data from 1733 adult patients with CIC randomized in two double-blind, placebo-controlled clinical trials (Study 1 and Study 2) to receive placebo or 3 mg of TRULANCE once daily for 12 weeks.

Most Common Adverse Reactions

Table 1 provides the incidence of adverse reactions reported in at least 2% of CIC patients in the TRULANCE-treated group and at an incidence that was greater than in the placebo group.

Table 1: Most Common Adverse Reactions^a in Two Placebo-Controlled Trials of TRULANCE [Study 1 and Study 2] in Patients with CIC

Adverse Reaction	TRULANCE, 3 mg (N = 863) %	Placebo (N = 870) %
Diarrhea	5	1

^a: Reported in at least 2% of TRULANCE-treated patients with CIC and at an incidence greater than placebo.

Diarrhea

The majority of reported cases of diarrhea occurred within 4 weeks of treatment initiation. Severe diarrhea was reported in 0.6% of TRULANCE-treated patients compared to 0.3% of placebo-treated patients. Severe diarrhea was reported to occur within the first 3 days of treatment [see *Warnings and Precautions (5.2)*].

Adverse Reactions Leading to Discontinuation

Discontinuations due to adverse reactions occurred in 4% of TRULANCE-treated patients and 2% of placebo-treated patients. The most common adverse reaction leading to discontinuation was diarrhea: 2% of TRULANCE-treated patients and 0.5% of placebo-treated patients withdrew due to diarrhea.

Less Common Adverse Reactions

Adverse reactions reported in less than 2% of TRULANCE-treated patients and at an incidence greater than placebo were: sinusitis, upper respiratory tract infection, abdominal distension, flatulence, abdominal tenderness, and increased liver biochemical tests (2 patients with alanine aminotransferase (ALT) greater than 5 to 15 times the upper limit of normal and 3 patients with aspartate aminotransferase (AST) greater than 5 times the upper limit of normal).

Irritable Bowel Syndrome with Constipation (IBS-C)

The safety data described below reflect data from 1449 adult patients with IBS-C randomized in two double-blind, placebo-controlled clinical trials (Study 3 and Study 4) to receive placebo or 3 mg TRULANCE once daily for 12 weeks.

Most Common Adverse Reactions

Table 2 provides the incidence of adverse reactions reported in at least 2% of IBS-C patients treated with TRULANCE and at an incidence that was greater than in the placebo group.

Table 2: Most Common Adverse Reactions^a in Two Placebo-Controlled Trials of TRULANCE [Study 3 and Study 4] in Patients with IBS-C

Adverse Reaction	TRULANCE, 3 mg (N = 723) %	Placebo (N = 726) %
Diarrhea ^b	4.3	1

^a: Reported in at least 2% of TRULANCE-treated patients with IBS-C and at an incidence greater than placebo.

^b: Verbatim reports of diarrhea were recorded as adverse reactions; reports of loose stools and increase in stool frequency were recorded as adverse reactions if they were also reported to be bothersome to the patient.

Diarrhea

The majority of reported cases of diarrhea occurred within 4 weeks of treatment initiation. Severe diarrhea was reported in 1% of TRULANCE-treated patients compared to 0.1% of placebo-treated patients [see Warnings and Precautions (5.2)]. Severe diarrhea was reported to occur within the first day of treatment.

Adverse Reactions Leading to Discontinuation

Discontinuations due to adverse reactions occurred in 2.5% of TRULANCE-treated patients and 0.4% of placebo-treated patients. The most common adverse reaction leading to discontinuation was diarrhea: 1.2% of TRULANCE-treated patients and 0% of placebo-treated patients withdrew due to diarrhea.

Less Common Adverse Reactions

Adverse reactions reported in 1% or more but less than 2% of TRULANCE-treated patients and at an incidence greater than placebo were: nausea, nasopharyngitis, upper respiratory tract infection, urinary tract infection, and dizziness. Two patients reported increased liver biochemical tests (alanine aminotransferase (ALT) greater than 5 to 15 times the upper limit of normal).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Plecanatide and its active metabolite are negligibly absorbed systemically following oral administration [see Clinical Pharmacology (12.3)] and maternal use is not expected to result in fetal exposure to the drug. The available data on TRULANCE use in pregnant women are not sufficient to inform any drug-associated risks for major birth defects and miscarriage. In animal developmental studies, no effects on embryo-fetal development were observed with oral administration of plecanatide in mice and rabbits during organogenesis at doses much higher than the recommended human dosage.

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

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.