



Trulance® (plecanatide)

For adults with
Chronic Idiopathic Constipation (CIC)
or Irritable Bowel Syndrome with
Constipation (IBS-C)

PURSUE ANOTHER LEVEL OF RELIEF



Trulance can help you have **MORE** regular, well-formed bowel movements, **LESS** IBS-C related abdominal pain and **LOW** incidence of diarrhea.*

*In a clinical trial vs placebo

What Is Trulance?

Trulance® (plecanatide) 3 mg tablets is a prescription medicine used in adults to treat Irritable Bowel Syndrome with Constipation (IBS-C) and Chronic Idiopathic Constipation (CIC). Chronic means the constipation is long lasting. "Idiopathic" means the cause of the constipation is unknown. **It is not known if Trulance is safe and effective in children less than 18 years of age.**

What is the Most important information I should know about Trulance?

- Do not give Trulance to children who are less than 6 years of age. It may harm them.
- You should not give Trulance to children 6 years to less than 18 years of age. It may harm them.
- Do not take Trulance if a doctor has told you that you have a bowel blockage (intestinal obstruction).

Please see additional Important Safety Information on the following pages and click here for [full Prescribing Information with Medication Guide](#).

What is Constipation?

You're not alone. Constipation is something that everyone has likely experienced at one time or another. Two common types of constipation are Chronic Idiopathic Constipation (CIC) and Irritable Bowel Syndrome with Constipation (IBS-C).

Symptoms of constipation

Constipation symptoms may include infrequent or hard-to-pass bowel movements, bloating, straining, discomfort, and never really feeling empty. While CIC and IBS-C share many of these same symptoms, there are important differences between the two.

CIC

A condition where patients suffer with the symptoms listed above for prolonged periods of time without a known cause.

"Chronic" means the constipation is long-lasting or keeps coming back. "Idiopathic" means the cause of the constipation is unknown.



1 in 7

U.S. adults have CIC

IBS-C

In addition to symptoms of chronic constipation, patients with IBS-C also have abdominal pain.



1 in 20

Adults have IBS-C

Talk to your healthcare provider

While it might seem awkward to talk about, telling your doctor which type or types of stool you typically have can help you both create a treatment plan that works for you and your body.

To help get the conversation started, let your doctor know:

1. Which of these constipation symptoms have you experienced?

- | | |
|--|---|
| <input type="checkbox"/> Fewer than 3 bowel movements a week | <input type="checkbox"/> Straining |
| <input type="checkbox"/> Hard-to-pass bowel movements | <input type="checkbox"/> Not feeling empty after a bowel movement |
| <input type="checkbox"/> Abdominal pain | <input type="checkbox"/> Other |

2. How long have you been trying to manage your symptoms?

- | | |
|--------------------------------------|------------------------------------|
| <input type="checkbox"/> 0-6 months | <input type="checkbox"/> 2-4 years |
| <input type="checkbox"/> 6-12 months | <input type="checkbox"/> 4+ years |
| <input type="checkbox"/> 1-2 years | |

3. Which types of stool from the Bristol Stool Form Scale on the left have you most frequently experienced when not taking medication?

- | | |
|---------------------------------|---------------------------------|
| <input type="checkbox"/> Type 1 | <input type="checkbox"/> Type 5 |
| <input type="checkbox"/> Type 2 | <input type="checkbox"/> Type 6 |
| <input type="checkbox"/> Type 3 | <input type="checkbox"/> Type 7 |
| <input type="checkbox"/> Type 4 | |

Then be sure to ask these simple questions:

1. What consistency should my stool be?
2. How many bowel movements a week should I be having?
3. Could Trulance help manage my constipation?

Want a more customized discussion tool?
 Visit [Trulance.com/DDG](https://www.trulance.com/DDG) to create your personalized Doctor Discussion Guide.

Please see additional Important Safety Information on the following pages and click here for [full Prescribing Information with Medication Guide](#).

The importance of stool form

The Bristol Stool Form is a visual representation of the 7 different types of Bowel Movements that you can have. A '4' bowel movement - described by the scale as smooth, soft sausage or snake shaped - is free of lumps or excess liquid and is considered well formed. A "Type 1 or 2" is often considered constipation while a "Type 6 or 7" is often considered diarrhea.

BRISTOL STOOL FORM SCALE

Type #1

Separate hard lumps, like nuts (hard to pass).



Type #2

Sausage-shaped but lumpy.



Type #3

Like a sausage but with cracks on surface.



Type #4

Like a sausage or snake, smooth & soft.



Type #5

Soft blobs with clear-cut edges.



Type #6

Fluffy pieces with ragged edges, a mushy stool.



Type #7

Watery, no solid pieces (entirely liquid).



Adapted from Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32:920-924.

SELECT IMPORTANT SAFETY INFORMATION

Before you take Trulance, tell your doctor:

- If you have any other medical conditions.
- If you are pregnant or plan to become pregnant. It is not known if Trulance will harm your unborn baby.

What is Trulance®?

Whether you've just been diagnosed or have been dealing with CIC or IBS-C for a while, Trulance can help you have **MORE**, regular, well-formed bowel movements versus placebo (sugar-pill) group.

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Trulance®
(plecanatide)

Trulance can help you have MORE, regular, well-formed bowel movements*

*Versus placebo (sugar-pill) group

Trulance was tested on patients over a 12-week study period.

Before entering the study,

- Patients had 2 spontaneous bowel movements (any bowel movement) in a week. Trulance helped patients have 5 spontaneous bowel movements in one week
- Patients had around one complete spontaneous bowel movements (bowel movement with a sensation of complete evacuation) in 3 weeks. Trulance helped people have 3 complete bowel movements in one week



Trulance helped people have "Normal" (smooth, soft sausage or snake shaped) stool or bowel movement form



Trulance can help provide relief from your constipation in as little as 24 hours.*

*In clinical studies, results seen without the use of laxatives.

For people with IBS-C, Trulance helped patients have LESS stomach (abdominal) pain



SELECT IMPORTANT SAFETY INFORMATION

Before you take Trulance, tell your doctor (cont'd):

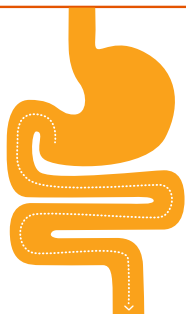
- If you are breastfeeding or plan to breastfeed. It is not known if Trulance passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take Trulance.
- **About all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Please see additional Important Safety Information on the following pages and click here for [full Prescribing Information with Medication Guide](#).

 To learn more, go to [Trulance.com](https://www.Trulance.com)

How does Trulance work, and what makes it different?

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Trulance®
(plecanatide)



Trulance is designed to act like the natural uroguanylin in your body—helping to provide the appropriate amount of fluid in the intestines.



SELECT IMPORTANT SAFETY INFORMATION

What are the common side effects of Trulance?

Diarrhea is the most common side effect and can sometimes be severe. Diarrhea often begins within the first 4 weeks of Trulance treatment. Stop taking Trulance and call your doctor right away if you get severe diarrhea.

These are not all the possible side effects of Trulance. Tell your doctor if you have any side effect that bothers you or that does not go away.

 To learn more, go to [Trulance.com](https://www.Trulance.com)

Trulance replicates what bodies may do naturally*

Trulance is the first medication for CIC and IBS-C that's designed to work like a natural peptide in your body called uroguanylin (pronounced "yur-oh-gwah-nih-lin"). To best understand how uroguanylin works, let's take a closer look at what happens in your body during the process of digestion.

- **After you eat, food is broken down in the stomach and the intestines**
- **In the process of digestion, fluid helps to form the consistency of the stool**
- **When there is too little fluid, it may result in constipation, while too much may result in diarrhea**
- **Uroguanylin is found in the GI tract and works best in the small intestine where—based on the changing pH levels of this area—it provides the appropriate amount of fluid to create well-formed stool***
- **Uroguanylin has also been shown to reduce abdominal pain***

***This activity was seen in animal studies. The relevance to humans is not yet known.**

What's the difference between Trulance and uroguanylin?

Trulance is very similar to the uroguanylin that your body naturally makes, with the exception of a single small change in the Trulance molecule that improves how it attaches in the small intestine.

By replicating the activity of uroguanylin, Trulance may also work to provide the appropriate amount of fluid for well-formed stool and to decrease abdominal pain in patients with IBS-C. The benefits and safety of Trulance have been well studied for both CIC and IBS-C.

Please see additional Important Safety Information on the following pages and click here for [full Prescribing Information with Medication Guide](#).

What do I need to know before taking Trulance?

Trulance is a once-daily medication for adults with CIC or IBS-C



Once-daily tablet



Any time of day



With or without food

ICD-10 codes*

K58.1	Irritable bowel syndrome with constipation
K59.04	Chronic idiopathic constipation

- Does not contain lactose or gluten

Getting the most out of Trulance

For best results, it's important to take Trulance every day or as directed by your doctor.

Remember that results can vary and relief can happen more quickly for some people than for others.

 To learn more, go to [Trulance.com](https://www.Trulance.com)

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Trulance®
(plecanatide)

Trulance can be taken any time of the day, with or without food

You shouldn't have to plan your day around your medication. Trulance helps you take control of your schedule with flexible dosing.

The safety of Trulance has been well studied

Less than or equal to 5% people experienced diarrhea versus 1% in placebo group.

Not a valid prescription, for illustrative purpose only.



SELECT IMPORTANT SAFETY INFORMATION

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

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- You should not give Trulance to children 6 years to less than 18 years of age. It may harm them.
- Do not take Trulance if a doctor has told you that you have a bowel blockage (intestinal obstruction).

Please see additional Important Safety Information on the following pages and click here for [full Prescribing Information with Medication Guide](#).

What Is Trulance?

Trulance® (plecanatide) 3 mg tablets is a prescription medicine used in adults to treat Irritable Bowel Syndrome with Constipation (IBS-C) and Chronic Idiopathic Constipation (CIC). Chronic means the constipation is long lasting. "Idiopathic" means the cause of the constipation is unknown. **It is not known if Trulance is safe and effective in children less than 18 years of age.**

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- Do not take Trulance if a doctor has told you that you have a bowel blockage (intestinal obstruction).

Before you take Trulance, tell your doctor:

- If you have any other medical conditions.
- If you are pregnant or plan to become pregnant. It is not known if Trulance will harm your unborn baby.
- If you are breastfeeding or plan to breastfeed. It is not known if Trulance passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take Trulance.
- **About all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

What are the common side effects of Trulance?

Diarrhea is the most common side effect and can sometimes be severe. Diarrhea often begins within the first 4 weeks of Trulance treatment. Stop taking Trulance and call your doctor right away if you get severe diarrhea.

These are not all the possible side effects of Trulance. Tell your doctor if you have any side effect that bothers you or that does not go away.

You are encouraged to report side effects to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088 or you can report side effects to Bausch Health at 1-877-361-2719.

Please see additional Important Safety Information on the following pages and click here for [full Prescribing Information with Medication Guide](#).



To learn more, go to Trulance.com

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Trulance®
(plecanatide)

Trulance Savings Card

Eligible* commercially insured patients may pay as little as **\$25 for up to a 90-day supply** of Trulance.

Enroll in the
Savings Card
program by visiting
Trulance.com/savings

Need help paying for your prescription?
Contact 888-869-8869 to see if you are eligible for additional financial assistance support.



Please see additional Important Safety Information on the following pages and click here for [full Prescribing Information with Medication Guide](#).

*See terms and conditions on back cover.

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Trulance®
(plecanatide)



- Eligible*, commercially insured patients may have a copay as low as \$25 for up to a 90-day supply

Pay as little as \$25* for up to a 90-day supply

To get your Trulance Savings, simply do the following:

1. Get a prescription for Trulance
2. Obtain a Trulance savings card from your doctor's office or print a card at Trulance.com/Savings
3. Follow the instructions at Trulance.com/Savings to activate your card

****TERMS AND CONDITIONS:** Patient is not eligible if he/she participates in, seeks reimbursement or submits a claim for reimbursement to any federal or state healthcare program with prescription drug coverage, such as Medicaid, Medicare, Medigap, VA, DOD, TRICARE, or any similar federal or state healthcare program (each a Government Program), or where prohibited by law. Patient must be enrolled in, and must seek reimbursement from or submit a claim for reimbursement to, a commercial insurance plan. Offer excludes full-cash-paying patients. To qualify for this offer, the patient's out-of-pocket expense must be a minimum of \$25 per prescription. Maximum savings limit applies; patient out-of-pocket expense may vary. Must be 18 years of age or older and under the age of 65 to participate in the program. This offer is good only in the US and Puerto Rico and is void where prohibited by law. Please see full program terms, conditions, and eligibility criteria at Trulance.com. Offer is valid for up to 12 prescription fills per year.

SELECT IMPORTANT SAFETY INFORMATION

- **Do not give Trulance to children who are less than 6 years of age. It may harm them.**
- **You should not give Trulance to children 6 years to less than 18 years of age. It may harm them.**
- Do not take Trulance if a doctor has told you that you have a bowel blockage (intestinal obstruction).

Please see additional Important Safety Information on the following pages and click here for [full Prescribing Information with Medication Guide](#).



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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® (plicanatide) 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, plicanatide 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)

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)

DOSE 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)

FULL PRESCRIBING INFORMATION: CONTENTS*	
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1	INDICATIONS AND USAGE
2	DOSE AND ADMINISTRATION
2.1	Recommended Dosage
2.2	Preparation and Administration Instructions
3	DOSE 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

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 plicanatide 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	DOSE 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 <i>Clinical Pharmacology</i> (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:

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

Oral Administration in Water:

- Place the TRULANCE tablet in a clean cup.
- Pour approximately 30 mL of room temperature water into the cup.
- Mix by gently swirling the tablet and water mixture for at least 10 seconds. The TRULANCE tablet will fall apart in the water.
- Swallow the entire contents of the tablet water mixture immediately.
- 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.
- Do not store the tablet-water mixture for later use.

Administration with Water via a Nasogastric or Gastric Feeding Tube:

- Place the TRULANCE tablet in a clean cup with 30 mL of room temperature water.
- Mix by gently swirling the tablet and water mixture for at least 15 seconds. The TRULANCE tablet will fall apart in the water.

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.	
DOSE 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 (≥2%) is diarrhea. (6.1)	

To report **SUSPECTED ADVERSE REACTIONS**, contact **Salix Pharmaceuticals** at 1-800-321-4576 or **FDA** at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2020	
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*Sections or subsections omitted from the full prescribing information are not listed.

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	DOSE FORMS AND STRENGTHS
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 <i>Warnings and Precautions</i> (5.1), <i>Use in Specific Populations</i> (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), plicanatide 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 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) %
	5	1

* 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 distention, 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 adults patients with IBS-C randomized in two double-blind, placebo-controlled clinical trials (Study 3 and Study 4) to receive placebo or 3 mg of 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* 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) %
	4.3	1

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

† 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

Plicanatide 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 plicanatide 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 defects, and of other adverse outcomes in human fetuses. In animal studies, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal data

Pregnant mice and rabbits were administered plicanatide during the period of organogenesis. There was no evidence of harm to embryo-fetal development at oral doses up to 800 mg/kg/day in mice and 250 mg/kg/day in rabbits. Oral administration of up to 600 mg/kg/day in mice during organogenesis through lactation produced no developmental abnormalities or effects on growth, learning and memory, or fertility in the offspring through maturation.

The maximum recommended human dose is approximately 0.05 mg/kg/day, based on a 60-kg body weight. Limited systemic exposure to plicanatide was achieved in animals during organogenesis [area under the plasma concentration-time curve (AUC)] = 449 ng•h/mL in rabbits given 250 mg/kg/day]. Plicanatide and its active metabolite are negligibly absorbed systemically following oral administration of the recommended human dosage. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

8.2 Lactation

Risk Summary

There is no information regarding the presence of plicanatide in human milk, or its effects on milk production or the breastfed infant. No lactation studies in animals have been conducted. Plicanatide and its active metabolite are negligibly absorbed systemically following oral administration [see *Clinical Pharmacology* (12.3)].

It is unknown whether the negligible systemic absorption of plicanatide at adults will result in a clinically relevant exposure to breastfed infants. Exposure to plicanatide in breastfed infants has the potential for serious adverse effects [see *Use in Special Populations* (8.4)]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRULANCE and any potential adverse effects on the breastfed infant from TRULANCE or from the underlying maternal condition.

8.4 Pediatric Use

TRULANCE is contraindicated in pediatric patients less than 6 years of age. Avoid use of TRULANCE in patients 6 years to less than 18 years of age [see *Contraindications* (4), *Warnings and Precautions* (5.1)]. The safety and effectiveness of TRULANCE in patients less than 18 years of age have not been established.

In nonclinical studies, deaths occurred within 24 hours in young juvenile mice (human age equivalent of approximately 1 month to less than 2 years) following oral administration of plicanatide, as described below in *Juvenile Animal Toxicity Data*. Because of 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 diarrhea and its potentially serious consequences. TRULANCE is contraindicated in patients less than 6 years of age. Given the deaths in young juvenile 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.

Juvenile Animal Toxicity Data

Single oral doses of plicanatide at 0.5 mg/kg and 10 mg/kg caused mortality in young juvenile mice on postnatal days 7 and 14, respectively (human age equivalent of approximately 1 month to less than 2 years). Treatment-related increases in the wetness of the stool contents were observed in juvenile mice following single doses of plicanatide on postnatal day 14 (human age equivalent of approximately less than 2 years), consistent with increased fluid in the intestinal lumen. Although the recommended human dose is approximately 0.05 mg/kg/day, based on a 60-kg body weight, mice and juvenile mice are not measurable in adult human toxicity, whereas systemic absorption was demonstrated in the juvenile animal toxicity studies. Animal and human doses should not be compared directly for evaluating relative exposure.

8.5 Geriatric Use

Chronic Idiopathic Constipation (CIC)

Of 2601 subjects in placebo-controlled clinical trials of TRULANCE, 273 (10%) were 65 years of age and over, and 47 (2%) were 75 years and over. Clinical studies of TRULANCE did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from patients 18 years or less than 65 years of age.

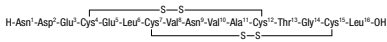
Irritable Bowel Syndrome with Constipation (IBS-C)

Of 1621 subjects in the placebo-controlled clinical studies of TRULANCE, 134 (8.3%) were 65 years of age and over, and 25 (1.5%) were 75 years and over. Clinical studies of TRULANCE did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from patients 18 years or less than 65 years of age.

11 DESCRIPTION

TRULANCE (plicanatide) is a guanylate cyclase-C (GC-C) agonist. Plicanatide is a 16 amino acid peptide with the following chemical name: L-Leucine, L-asparaginy-L-o-aspartyl-L-o-glutamyl-L-cysteinyl-L-o-glutamyl-L-leucyl-L-cysteinyl-L-valyl-L-asparaginy-L-valyl-L-alanyl-L-cysteinyl-L-threonylglycyl-L-cysteinyl-, cyclic (4 → 12), (7 → 15)-bis(disulfide).

The molecular formula of plicanatide is C₁₆H₂₆N₁₆O₁₆S₈, and the molecular weight is 1682 Daltons. The amino acid sequence for plicanatide is shown below.



The solid lines linking cysteines illustrate disulfide bridges.

Plicanatide is an amorphous, white to off-white powder. It is soluble in water. TRULANCE tablets are supplied as 3 mg tablets for oral administration. The inactive ingredients are magnesium stearate and microcrystalline cellulose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Plicanatide is a structural analog of human uroguanylin, and similarly to uroguanylin, plicanatide functions as a guanylate cyclase-C (GC-C) agonist. Both plicanatide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation of extracellular cGMP has been associated with a decrease in the activity of pain-sensing nerves in animal models of visceral pain. Elevation of intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit. In animal models, plicanatide has been shown to increase fluid secretion into the gastrointestinal (GI) tract, accelerate intestinal transit, and cause changes in stool consistency.

In an animal model of visceral pain, plicanatide reduced abdominal muscle contractions, a measure of intestinal pain.

12.2 Pharmacodynamics

Food Effect

Subjects who received either a low-fat, low-calorie (L-F-LC) meal or a high-fat, high-calorie meal (H-F-HC) meal reported looser stools than faster subjects up to 24 hours after a single dose of TRULANCE 9 mg (3 times the recommended dose). In clinical studies, TRULANCE was administered with or without food [see *Dosage and Administration* (2.2)].

12.3 Pharmacokinetics

Absorption

Plicanatide was minimally absorbed with negligible systemic availability following oral administration. Concentrations of plicanatide and its active metabolite in plasma were below the limit of quantitation in the majority of analyzed plasma samples after an oral TRULANCE dose of 3 mg. Therefore, standard pharmacokinetic parameters such as AUC, maximum concentration (C_{max}), and half-life (t_{1/2}) could not be calculated.

Food Effect

In a crossover study, 24 healthy subjects were given a single dose of TRULANCE 9 mg (3 times the recommended dose) in 3 different states: fasted; following a low-fat, low-calorie meal (L-F-LC; approximately 350 calories: 17% from fat, 66% from carbohydrate, and 17% from protein); and following a high-fat, high-calorie meal (H-F-HC; approximately 1000 calories: 50% from fat, 25% from carbohydrate, and 15% from protein). Plicanatide was detected in 1 subject (fasted state) at 0.5 and 1 hour post-dose. Plicanatide concentrations were below the limit of quantitation for all other time points and for all other subjects. The active metabolite was not detected in any subject.

Distribution

Given that plicanatide concentrations following clinically relevant oral doses were not measurable, plicanatide is expected to be minimally distributed in tissues. Oral plicanatide was localized to the GI tract where it exerted its effects as a GC-C agonist with negligible systemic exposure. Plicanatide exhibited little to no binding to human serum albumin or human α-1-acid glycoprotein.

<div>Medication Guide</div> <div>TRULANCE® (TROO lanns)</div> <div>(plecanatide) tablets</div>
<div>What is the most important information I should know about TRULANCE?</div> <div><ul style="list-style-type: none">• Do not give TRULANCE to children who are less than 6 years of age. It may harm them.• You should not give TRULANCE to children 6 years to less than 18 years of age. It may harm them.</div> <div>See “What are the possible side effects of TRULANCE?” for more information about side effects.</div>
<div>What is TRULANCE?</div> <div>TRULANCE is a prescription medicine used in adults to treat:</div> <div><ul style="list-style-type: none">• a type of constipation called chronic idiopathic constipation (CIC). Idiopathic means the cause of the constipation is unknown.• irritable bowel syndrome with constipation (IBS-C).</div> <div>It is not known if TRULANCE is safe and effective in children less than 18 years of age.</div>
<div>Who should not take TRULANCE?</div> <div><ul style="list-style-type: none">• Do not give TRULANCE to children who are less than 6 years of age.• Do not take TRULANCE if a doctor has told you that you have a bowel blockage (intestinal obstruction).</div>
<div>Before taking TRULANCE, tell your doctor about all of your medical conditions, including if you:</div> <div><ul style="list-style-type: none">• are pregnant or plan to become pregnant. It is not known if TRULANCE will harm your unborn baby.• are breastfeeding or plan to breastfeed. It is not known if TRULANCE passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take TRULANCE.</div> <div>Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.</div>
<div>How should I take TRULANCE?</div> <div><ul style="list-style-type: none">• Take TRULANCE exactly as your doctor tells you to take it.• Take TRULANCE by mouth, 1 time each day with or without food.• If you miss a dose, skip the missed dose. Take the next dose at your regular time. Do not take 2 doses at the same time.• TRULANCE tablets should be swallowed whole.<ul style="list-style-type: none">◦ Adults who cannot swallow TRULANCE tablets whole may crush the TRULANCE tablet and mix with applesauce or dissolve TRULANCE in water before swallowing. TRULANCE tablets may also be taken with water by adults through a nasogastric or gastric feeding tube.</div> <div>It is not known if TRULANCE is safe and effective when crushed and mixed with other foods or dissolved in other liquids.</div>
<div>Taking TRULANCE in applesauce:</div> <div><ul style="list-style-type: none">• Crush the TRULANCE tablet in a clean container until it is a powder and mix with 1 teaspoon of room temperature applesauce.• Swallow all of the TRULANCE and applesauce mixture right away. Do not keep the TRULANCE and applesauce mixture for future use.</div>
<div>Taking TRULANCE in water:</div> <div><ul style="list-style-type: none">• Place the TRULANCE tablet in a clean cup and pour 1 ounce (30 mL) of room temperature water into the cup.• Gently swirl the TRULANCE tablet and water for at least 10 seconds. The TRULANCE tablet will fall apart in the water.• Swallow all of the TRULANCE tablet and water mixture right away. Do not keep the mixture for future use.• If you see any part of the tablet left in the cup, add another 1 ounce (30 mL) of water to the cup, swirl for at least 10 seconds, and swallow right away.</div>
<div>Taking TRULANCE through a nasogastric or gastric feeding tube:</div> <div>Gather the supplies you will need to take your TRULANCE dose. Your doctor should tell you what size catheter tip syringe you will need for your dose. Ask your doctor if you have any questions about how to give TRULANCE the right way.</div> <div><ul style="list-style-type: none">• Place the TRULANCE tablet in a clean cup with 1 ounce (30 mL) of room temperature water.• Gently swirl the TRULANCE tablet and water for at least 15 seconds. The TRULANCE tablet will fall apart in the water.• Flush the nasogastric or gastric feeding tube with 1 ounce (30 mL) of water.• Draw up the TRULANCE tablet and water mixture into a catheter tip syringe and give right away through the nasogastric or gastric feeding tube. Do not keep the mixture for future use.• If you see any part of the tablet left in the cup, add another 1 ounce (30 mL) of water to the cup, swirl for at least 15 seconds and use the same catheter tip syringe to give the mixture through the nasogastric or gastric feeding tube.• Using the same or another catheter tip syringe, flush the nasogastric or gastric feeding tube with at least 10 mL of water.</div>
<div>What are the possible side effects of TRULANCE?</div> <div>TRULANCE can cause serious side effects, including:</div> <div><ul style="list-style-type: none">• See “What is the most important information I should know about TRULANCE?”• Diarrhea is the most common side effect of TRULANCE, and it can sometimes be severe.<ul style="list-style-type: none">◦ Diarrhea often begins within the first 4 weeks of TRULANCE treatment.</div> <div>Stop taking TRULANCE and call your doctor if you develop severe diarrhea.</div> <div>These are not all the possible side effects of TRULANCE.</div> <div>Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.</div>

