

QUESTIONS-ANSWERS

ABOUT ^{Pr} **Zaxine550[®]** for IBS-D rifaximin 550 mg tablets

Indicated for the treatment of IBS-D



What is IBS-D?

IBS-D is a subtype of IBS. The Rome II criteria for the diagnosis of IBS are:¹

- Abdominal discomfort or pain for ≥ 12 weeks (not necessarily consecutive) in the preceding 12 months associated with ≥ 2 of the following:
 1. Relieved with defecation
 2. Onset associated with a change in frequency of stool
 3. Onset associated with a change in form (appearance) of stool

Possible cause

Microbiota in the GI track are believed to play

an important role in the development of the symptoms associated with IBS-D. It has been shown that an acute GI infection can **increase the odds by 6-fold of developing IBS**. It is suggested that a dysbiosis in the microbiome can lead to increased bloating by way of:^{1*}

- Increased fermentation/gas
- Small intestinal bacterial overgrowth
- Mucosal irritation and
- Minimal chronic localized inflammation in the gut

* Clinical significance has not been established.

What is ZAXINE?

ZAXINE (rifaximin) is a minimally absorbed antibacterial agent.

Indication

ZAXINE is indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.¹

How does ZAXINE work in IBS-D?

ZAXINE acts locally on the microflora of the gut.*

Primary mode of action^{1*}

- ↓ Reduces bacterial load and bacterial products that can negatively affect the host
- ↑ Alleviates the most common IBS-D symptoms, including bloating, abdominal pain and diarrhea

A sustained effect in IBS-D has been observed following a 2-week treatment course with rifaximin. This suggests that rifaximin may

affect the underlying causes of IBS-D mediated by bacterial dysbiosis.*

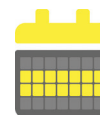
- Should not be used for the treatment of systemic bacterial infections.
- Effect on gut microbiota may reduce the local immune responses and, by suppressing the effect of bacterial endotoxins helping to prevent dysbiosis, maintain homeostasis and mucosal integrity.*
- May also modulate the patient's local immune responses directly via the PXR pathway; it has been shown to reduce and reverse local mucosal inflammation.*

GI=gastrointestinal

* Clinical significance has not been established.

What is the recommended dosing for ZAXINE?

- ➔ 1 tablet
- ➔ 3 times per day
- ➔ for 14 days



- Can be taken **with or without** food.
- In the IBS-D clinical trials, patients who experienced a recurrence of symptoms and who responded to a first treatment were generally safely and **effectively retreated for up to 2 times**.¹
 - Current clinical trials have not evaluated the safety and efficacy of ≥ 3 repeat treatments for IBS-D.¹

Please consult the Product Monograph for complete dosing information.

How effective was the 14-day treatment of ZAXINE in clinical trials?

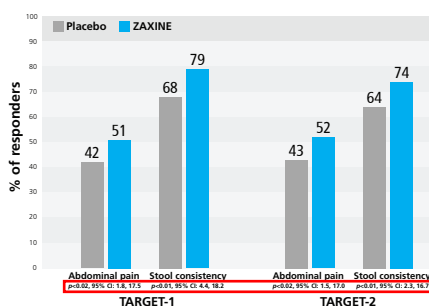
ZAXINE demonstrated efficacy in providing relief in IBS-D symptoms, such as abdominal pain and diarrhea.

DEMONSTRATED EFFICACY IN IBS-D WITH 14-DAY TREATMENT (TARGET 1 and TARGET 2)^{††}

During the month following 2 weeks of treatment in the TARGET 1 and TARGET 2 studies, respectively:

- Significantly more patients taking ZAXINE **experienced adequate relief of IBS symptoms** (as measured by a weekly Subject Global Assessment question) vs. those taking placebo (SGA-IBS weekly results: 41% vs. 31%, $p=0.0125$ and 41% vs. 32%, $p=0.0263$, respectively).

Significantly more ZAXINE patients were monthly responders for the endpoint of IBS-related abdominal pain and stool consistency vs. placebo (secondary endpoints)^{††}



- Patients were monthly responders if they experienced a $\geq 30\%$ decrease from baseline in abdominal pain for ≥ 2 weeks during the month following 2 weeks of treatment and had a weekly mean stool consistency score < 4 (loose stool) for ≥ 2 weeks during the month following 2 weeks of treatment.

Adapted from Product Monograph¹

† TARGET 1 and TARGET 2 were double-blind, placebo-controlled studies in which 1258 patients meeting Rome II criteria for IBS were randomized to ZAXINE 550 mg three times a day (n=624) or placebo (n=634) for 14 days and were then followed for a 10-week treatment-free period. Rome II Criteria: At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features: 1. Relieved with defecation; and/or 2. Onset associated with a change in frequency of stool; and/or 3. Onset associated with a change in form (appearance) of stool. The primary endpoint was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least 2 of 4 weeks during the month following 14 days of treatment. Adequate relief was defined as a response of "yes" to the following weekly Subject Global Assessment (SGA) question: "In regards to your IBS symptoms, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms?"

How effective was repeat treatment of ZAXINE in the TARGET 3 clinical trial?

REPEAT TREATMENT (TARGET 3):^{1*}

TARGET 3 evaluated repeat treatment with ZAXINE in adults with IBS-D meeting Rome III criteria for up to 46 weeks.

In this trial, patients who experienced a recurrence of symptoms and who responded to a first treatment were safely and effectively retreated for up to 2 times.¹

- ➔ 2579 patients were enrolled to receive open-label ZAXINE for 14 days, followed by 4 weeks of treatment-free follow-up.
- ➔ 1074 (44%) patients responded to initial treatment and were evaluated over 22 weeks for continued response or recurrence of IBS-symptoms.
- ➔ Of the patients who responded to open-label ZAXINE, **382 (36%) experienced a period of symptom inactivity or decrease that did not require repeat treatment by the time** they discontinued, including patients who completed the 22 weeks after initial treatment with ZAXINE.
- ➔ A total of 636 patients subsequently had signs and symptoms recurrence and were randomized to the repeat treatment phase.
- ➔ The median time to recurrence for patients who experienced initial response during the open-label phase with ZAXINE was 10 weeks (range 6 to 24 weeks).
- The subsequent double-blind, placebo-controlled portion of the trial evaluated the primary endpoint, proportion of patients who were responders to repeat treatment.
- The ZAXINE and placebo groups had similar baseline IBS symptom scores at the time of recurrence and randomization to the double blind phase, but symptom scores were less severe than at study entry into the open-label phase.



Significantly more ZAXINE patients were responders vs. placebo¹

- More patients receiving ZAXINE were monthly responders for abdominal pain and stool consistency vs. placebo (33% vs. 25%, respectively, $p < 0.05$, 95% CI 0.6-14.6%).

➔ Patients were considered responders if they were both weekly IBS-related abdominal pain responders and weekly stool consistency responders in a given week for ≥ 2 weeks during Weeks 3 to 6 in the double-blind first repeat treatment phase. Weekly responder in IBS-related abdominal pain was defined as $\geq 30\%$ improvement from baseline in the weekly average abdominal pain score. Weekly responder in stool consistency was defined as $\geq 50\%$ reduction in the number of days in a week with stool consistency of type 6 or 7 compared with baseline.

What is the safety profile for ZAXINE?

ZAXINE has a demonstrated safety profile.¹

Most commonly reported treatment-emergent adverse events reported at a higher rate than placebo in TARGET 1 and TARGET 2

Treatment period (during treatment with study drug)		
Adverse event, % (n)	ZAXINE (n=624)	placebo (n=634)
Nausea	2.6% (16)	1.9% (12)
Diarrhea	1.4% (9)	1.3% (8)
Overall evaluation period (during treatment with study drug + off-treatment intervals [follow-up + maintenance])		
Adverse event, % (n)	ZAXINE (n=624)	placebo (n=634)
Nausea	4.3% (27)	3.8% (24)
Diarrhea	4.3% (27)	3.5% (22)

Adapted from Product Monograph¹

- In TARGET 3, the adverse reactions that occurred at a frequency $>2\%$ in ZAXINE-treated patients (n=328) at a higher rate than placebo (n=308) during the double-blind treatment phase were ALT increased (ZAXINE 2%, placebo 1%) and nausea (ZAXINE 2%, placebo 1%).¹

**For more information, please visit www.zaxine.ca
Access code: Zaxine123**

Clinical use which has not been discussed elsewhere in this piece:

Studies specifically designed to determine the dose in elderly patients (>65 years of age) have not been performed. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Safety and effectiveness has not been investigated in children and adolescents <18 years of age.

Contraindications:

- Hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents

Relevant warnings and precautions which have not been discussed elsewhere in this piece:

- Potential for increased systemic exposure to rifaximin in disease states in which intestinal barrier function or gut motility is altered
- Clostridium difficile-associated disease (CDAD) has been reported with use of nearly all antibacterial agents, including ZAXINE, and may range in severity from mild diarrhea to fatal colitis. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality. Careful medical history is necessary. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.
- Not recommended in patients with intestinal obstruction
- Caution in patients with severe (Child-Pugh C) hepatic impairment
- Discontinue if a severe hypersensitivity reaction occurs
- Pharmacokinetics not studied in impaired renal function
- Not for use during pregnancy
- Unknown if ZAXINE is excreted in human milk; a decision should be made whether to discontinue nursing or to discontinue the drug
- Possible relationship between treatment and carcinogenicity cannot be ruled out

For more information:

Please consult the Product Monograph at <https://health-products.canada.ca/dpd-bdpp/index-eng.jsp> for important information relating to adverse reactions, drug interactions and dosing which have not been discussed in this piece. The Product Monograph is also available by calling 1-844-587-4623.

* Rome III Criteria: Recurrent abdominal pain or discomfort (uncomfortable sensation not described as pain) ≥ 3 days month in last 3 months associated with ≥ 2 of the following: 1) Improvement with defecation; 2) Onset associated with a change in frequency of stool; 3) Onset associated with a change in form (appearance) of stool. During the open-label phase, patients were considered responders if they simultaneously met the weekly response criteria during ≥ 2 of the 4 weeks after treatment for the following: $\geq 30\%$ improvement from baseline in the weekly average abdominal pain score based on the daily question: "In regards to your specific IBS symptoms of abdominal pain, on a scale of 0-10, what was your worst IBS-related abdominal pain over the last 24 hours? "Zero" means you have no pain at all "Ten" means the worst possible pain you can imagine" and a $\geq 50\%$ reduction in the number of days in a week with a daily stool consistency of Bristol Stool Scale Type 6 or 7 compared with baseline, where 6=fluffy pieces with ragged edges, a mushy stool; 7=watery stool, no solid pieces; entirely liquid.

References

1. ZAXINE Product Monograph. Salix Pharmaceuticals, Inc., February 11, 2019.

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