PRODUCT MONOGRAPH

PrZAXINE

Rifaximin

550 mg tablets

Antibacterial agent

Manufactured by:

Salix Pharmaceuticals, Inc.
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U.S.A.

Date of Preparation:
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Distributed by:
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[Pr]ZAXINE

Rifaximin

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	550 mg tablet	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ZAXINE (rifaximin) is indicated for:

- the reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥18 years of age

In the trials of ZAXINE for HE, 91% of the patients were using lactulose concomitantly. Differences in the treatment effect of those patients not using lactulose concomitantly could not be assessed.

ZAXINE has not been studied in patients with MELD (Model for End-Stage Liver Disease) scores > 25, and only 8.6% of patients in the controlled trial had MELD scores over 19. There is increased systemic exposure to rifaximin in patients with hepatic dysfunction.

Geriatrics (> 65 years of age):

Studies specifically designed to determine the dose in elderly patients have not been performed. In the controlled trial with ZAXINE, 19.4% were aged 65 years and over, while 2.3% were 75 and over. 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.

Pediatrics (< 18 years of age):

The safety and effectiveness of ZAXINE in the prevention of overt hepatic encephalopathy (HE)

recurrence has not been investigated in children and adolescents under 18 years of age.

CONTRAINDICATIONS

ZAXINE (rifaximin) is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the ingredients in ZAXINE (See **DOSAGE FORMS, COMPOSITION AND PACKAGING** for a complete listing. See also **WARNINGS AND PRECAUTIONS** – **Immune**, and **ADVERSE REACTIONS**).

WARNINGS AND PRECAUTIONS

General

Not for Systemic Infections

ZAXINE (rifaximin) acts locally on the microflora of the gut and should not be used for the treatment of systemic bacterial infections.

Low systemic absorption of rifaximin has been noted in healthy individuals, but absorption is increased in subjects with impaired hepatic function. (See **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**). There is the potential for increased systemic exposure to rifaximin in disease states in which intestinal barrier function or gut motility is altered. Rifaximin exposure is slightly higher in patients with inflammatory bowel disease (2.3- and 4.3-fold increases in C_{max} and AUC, respectively) or irritable bowel syndrome (1.8- and 1.7-fold increases in C_{max} and AUC, respectively) than in healthy subjects receiving the same doses.

The effect on the gut flora following long-term use of rifaximin is not known.

Carcinogenicity

A possible relationship between Zaxine treatment and carcinogenicity cannot be ruled out. A 2 year rat study with administration of rifaximin alfa- at doses of 150 to 250 mg/kg/day (doses equivalent to1.3 to 2.2 times the recommended human dose, based on relative body surface area comparisons) showed an increased trend in malignant schwannomas of the heart in male rats, but not female rats. (See **TOXICOLOGY, Carcinogenicity**).

Gastrointestinal

Clostridium difficile-Associated Disease

Clostridium difficile-associated disease (CDAD) has been reported with use of nearly all antibacterial agents, including ZAXINE (see **ADVERSE REACTIONS**), and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon which may lead to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is

necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Intestinal Obstruction
Zaxine has not been studied for use in prevention of hepatic encephalopathy in patients with intestinal obstruction; use in patients with an intestinal obstruction is not recommended.

Hepatic/Biliary/Pancreatic
Following administration of ZAXINE 550 mg twice daily to patients with a history of hepatic encephalopathy, the systemic exposure to rifaximin was increased with increasing hepatic impairment. The AUC_{tau} was about 10-, 13-, and 20-fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively, compared to that in healthy subjects (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). The highest systemic exposure to rifaximin was seen in patients with severe hepatic impairment. Additionally the clinical trials were limited to patients with MELD scores <25. Therefore caution should be exercised when administering ZAXINE to patients with severe (Child-Pugh C) hepatic impairment.

Immune
Hypersensitivity Reactions
Acute hypersensitivity reactions, including dyspnea, rash, pruritus, angioedema and anaphylaxis, have been reported with rifaximin (see **ADVERSE REACTIONS**). If a severe hypersensitivity reaction occurs, ZAXINE should be discontinued and appropriate therapy should be instituted.

Renal
The pharmacokinetics of rifaximin in patients with impaired renal function have not been studied.

Special Populations
Pregnant Women:
There are no adequate and well controlled studies in pregnant women. ZAXINE tablets should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus.

Fetal rat malformations were observed in a study of pregnant rats administered a high dose of rifaximin that is equivalent to the therapeutic dose in patients with hepatic encephalopathy (based upon plasma AUC comparisons). Fetal rabbit malformations were observed from pregnant rabbits administered mid and high rifaximin doses that resulted in less than 0.1 times the dose in patients with hepatic encephalopathy, based upon plasma AUC comparisons. (See **TOXICOLOGY**).

Nursing Women:
It is not known whether ZAXINE is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions from ZAXINE in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age):
The safety and effectiveness of ZAXINE for HE have not been established in patients < 18 years of age.

Geriatrics (> 65 years of age):
In the controlled trial with ZAXINE for hepatic encephalopathy, 19.4% were 65 and over, while 2.3% were 75 and over. 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The most common adverse reactions in the clinical and post-marketing setting are GI-related (e.g. diarrhea, nausea), the most serious of which is *C. difficile*-associated diarrhea. Rash, pruritus, pyrexia, anemia, dyspnea, arthralgia, muscle spasms and peripheral edema were also commonly reported with rifaximin use (1-15 %) and were seen at a higher frequency than in the placebo group.

Clinical Trial Adverse Drug Reactions
> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The safety of rifaximin in patients in remission from hepatic encephalopathy (HE) was evaluated in two studies, a randomized, double-blind, placebo-controlled phase 3 study, RFHE3001, and a long-term, open-label study, RFHE3002.

Study RFHE3001 compared 140 patients treated with rifaximin (dose 550 mg twice daily for 6 months) to 159 patients treated with placebo, while study RFHE3002 treated 322 patients, of whom 152 were from the RFHE3001 study, with rifaximin 550 mg twice daily for 12 months (66% of patients) and for 24 months (39% of patients), for a median exposure of 512.5 days.

All adverse reactions that occurred in patients treated with rifaximin at an incidence ≥ 5% and at a higher incidence (≥ 1%) than placebo patients in RFHE3001 are reported in the following table.

Table 1: Adverse events occurring in ≥ 5% of patients receiving rifaximin and at a higher incidence than placebo in Study RFHE3001

MedDRA System Organ Class	Event	Placebo N = 159 n (%)	Rifaximin (550 mg BID) N = 140 n (%)
Blood and lymphatic system disorders	Anaemia	6 (3.8)	11 (7.9)
Gastrointestinal disorders	Ascites	15 (9.4)	16 (11.4)
	Nausea	21 (13.2)	20 (14.3)
	Abdominal pain upper	8 (5.0)	9 (6.4)
General disorders and administration site conditions	Oedema peripheral	13 (8.2)	21 (15.0)
	Pyrexia	5 (3.1)	9 (6.4)
Musculoskeletal and connective tissue disorders	Muscle spasms	11 (6.9)	13 (9.3)
	Arthalgia	4 (2.5)	9 (6.4)
Nervous system disorders	Dizziness	13 (8.2)	18 (12.9)
Psychiatric disorders	Depression	8 (5.0)	10 (7.1)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	7 (4.4)	9 (6.4)
Skin and subcutaneous tissue disorders	Pruritus	10 (6.3)	13 (9.3)
	Rash	6 (3.8)	7 (5.0)

Table 2 includes rifaximin adverse drug reactions (considered drug-related by the investigator) observed in the placebo-controlled study RFHE3001 and the long term study RFHE3002 at an incidence ≥ 1%.

Table 2: Drug-Related TEAEs in ≥ 1% of Rifaximin- or Placebo-Treated Subjects – (Study RFHE3001 and All Rifaximin Subjects from RFHE3001 and RFHE3002)

MedDRA System Organ Class Preferred Term	Event	RFHE3001		RFHE3001 and RFHE3002
		Placebo (N = 159) n (%)	Rifaximin 550 mg BID (N = 140) n (%)	All Rifaximin 550 mg BID (N = 392) n (%)
Gastrointestinal disorders	Diarrhea	11 (6.9)	5 (3.6)	9 (2.3)
	Nausea	12 (7.5)	4 (2.9)	10 (2.6)
	Abdominal distension	2 (1.3)	3 (2.1)	4 (1.0)
	Abdominal pain upper	3 (1.9)	2 (1.4)	4 (1.0)
	Abdominal pain	3 (1.9)	1 (0.7)	6 (1.5)
	Flatulence	3 (1.9)	1 (0.7)	5 (1.3)
	Vomiting	5 (3.1)	1 (0.7)	5 (1.3)
	Constipation	2 (1.3)	0	2 (0.5)
General disorders and administration site conditions	Fatigue	4 (2.5)	1 (0.7)	3 (0.8)
Infections and infestations	Clostridium colitis	0	2 (1.4)	2 (0.5)
Metabolism and nutrition disorders	Decreased appetite	2 (1.3)	0	0
Musculoskeletal and connective tissue disorders	Muscle spasms	2 (1.3)	5 (3.6)	6 (1.5)
Nervous system disorders	Dizziness	2 (1.3)	3 (2.1)	8 (2.0)
	Balance disorder	0	2 (1.4)	2 (0.5)
	Headache	5 (3.1)	2 (1.4)	2 (0.5)
	Hepatic encephalopathy	3 (1.9)	2 (1.4)	2 (0.5)
Psychiatric disorders	Insomnia	2 (1.3)	0	1 (0.3)
Skin and subcutaneous tissue disorders	Pruritus	3 (1.9)	2 (1.4)	2 (0.5)
	Rash	2 (1.3)	1 (0.7)	2 (0.5)

TEAE = treatment-emergent adverse event

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse reactions, presented by body system, have also been reported (from the placebo-controlled clinical trial RFHE3001 and the long term study RFHE3002) in < 1% of patients taking ZAXINE 550 mg taken orally two times a day for hepatic encephalopathy. The following includes adverse events, considered by the investigator to be drug-related:
Blood and lymphatic system disorders: Anaemia, coagulopathy
Ear and labyrinth disorders: Hypoacusis, tinnitus
Eye disorders: Conjunctivitis, visual acuity reduced

Gastrointestinal disorders: Abdominal pain, ascites, constipation, dyspepsia, dry mouth, faeces discoloured, stomach discomfort
General disorders and Administration Site Conditions: Asthenia, fatigue, oedema peripheral, pyrexia
Infections and Infestations: Infectious mononucleosis, Klebsiella bacteraemia, peritonitis bacterial
Injury, Poisoning and Procedural Complications: Fall
Metabolism and nutrition disorders: Anorexia, hypokalemia
Musculoskeletal, Connective Tissue, and Bone disorders: Back pain
Nervous System disorders: Amnesia, balance disorder, headache, hypogeusia, hyposmia
Psychiatric disorders: Anxiety, confusional state, disorientation, insomnia, mental status changes
Renal and urinary disorders: Dysuria
Skin and Subcutaneous Tissue disorders: Pruritus, rash, rash erythematous, swelling face, urticaria
Vascular disorders: Hot flush

Abnormal Hematologic and Clinical Chemistry Findings
No specific trends in abnormal hematologic or clinical chemistry findings have been reported.

Post-Market Adverse Drug Reactions
The following adverse reactions have been identified during post approval use of ZAXINE. Because these reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to either their seriousness, frequency of reporting or causal connection to ZAXINE.

Infections and Infestation: C. difficile-associated colitis
General: Hypersensitivity reactions, including exfoliative dermatitis, rash, angioneurotic edema (swelling of face and tongue and difficulty swallowing), urticaria, flushing, pruritus and anaphylaxis have been reported. These events occurred as early as within 15 minutes of drug administration.

DRUG INTERACTIONS

Overview
Rifaximin is a structural analog of rifampin, a rifamycin derivative. ZAXINE contains rifaximin-α, one of the polymorphic forms of rifaximin. Low systemic absorption of this alfa form has been noted in healthy individuals, but absorption is increased in subjects with impaired hepatic function, and to a lesser extent, in patients with inflammatory bowel disease and irritable bowel syndrome.

***In Vitro* Data**

In vitro studies in human hepatocytes have demonstrated:
Rifaximin is metabolized by CYP3A4.

Rifaximin is a weak inducer of CYP3A4 (at a concentration of 0.2 μM [157 ng/ml]). Rifaximin did not inhibit cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 at concentrations ranging up from 2 to 200 ng/mL.

An *in vitro* study suggested that rifaximin is a substrate of, and a weak inhibitor of P-glycoprotein (P-gp) (See **DETAILED PHARMACOLOGY**).

Table 3 summarizes the potential for drug-drug interactions with rifaximin.

Table 3 Established or Potential Drug-Drug Interactions for Rifaximin

Proper name	Reference	Effect	Clinical comment
CYP3A4 substrates (e.g. Midazolam)	CT	Rifaximin 550 mg bid x 7 or 14 days reduced oral midazolam AUC by 4 – 9%, and Cmax by 4-5% in healthy subjects	Rifaximin is a substrate and a weak inducer of CYP3A4 *in vitro*. No clinically significant effects on the pharmacokinetics of CYP3A4 substrates were found in healthy subjects; however, the effect of rifaximin on CYP3A4 substrates in subjects with hepatic impairment has not been evaluated. The drug could have an effect on the pharmacokinetics of concomitant CYP3A4 substrates (eg. warfarin, antiepileptics, antiarrhythmics) in hepatically impaired subjects who have elevated systemic levels of rifaximin.
P-gp inhibitors (e.g. Cyclosporine)	CT	Cyclosporine 600 mg increased C_{max} of rifaximin 83-fold and increased AUC 124-fold in healthy subjects	Concomitant drugs that inhibit P-gp could significantly increase the systemic exposure of rifaximin in hepatically impaired subjects, in particular in patients with severe hepatic impairment
P-gp substrates (e.g. Digoxin)	T	Rifaximin showed weak inhibition of digoxin transport *in vitro* at concentrations 100 times clinical Cmax in healthy subjects	Clinical relevance in hepatically impaired subjects is unknown
Oral Contraceptives - CYP3A4 substrate and potential for rifaximin-induced altered gut flora effect (e.g. ethinyl estradiol and norgestimate)	CT	After rifaximin 550 mg TID x 7 days in healthy volunteers, Cmax of OC minimally lowered, but no change in AUC of OC.	OC Cmax within clinically reported values. Clinical relevance of minimal C_{max} reduction in healthy volunteers and effects on contraception are unknown.

Proper name	Reference	Effect	Clinical comment
Warfarin	Case Study	A patient on rifaximin 400 mg TID x 10 days for small intestinal bacterial overgrowth, also on a stable warfarin dose, had elevated INR while on rifaximin.	Patient was on stable warfarin therapy, and when given rifaximin treatment for small intestinal bacterial overgrowth, anticoagulation was attenuated. This potential interaction has not been studied in a controlled clinical trial.

CT = Clinical Trial; T = Theoretical

Drug-Food Interactions
In healthy volunteers, administration of rifaximin within 30 minutes of a standardized high-fat breakfast increased C_{max} and AUC by approximately 1.2- and 2-fold, respectively.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Due to the limited systemic absorption of ZAXINE (rifaximin), no specific dosing adjustment is recommended for patients with mild to moderate hepatic insufficiency.

Although no dosage adjustment is recommended at this time, caution should be exercised when ZAXINE is administered to patients with severe (Child-Pugh C) hepatic impairment and in patients with MELD score ≥25 (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). While taking ZAXINE with food has resulted in small increases in systemic exposure in healthy subjects, the effects of food on ZAXINE exposure in hepatic impairment patients have not been studied. Therefore, it is recommended that hepatic impairment patients, particularly those with severe hepatic impairment, take ZAXINE without food.

Treatment duration beyond 6 months should take into consideration the individual balance between benefits and risks, including those associated with the progression of hepatic dysfunction and increasing systemic exposure to rifaximin.

Recommended Dose and Dosage Adjustment
The recommended dose of ZAXINE is one 550 mg tablet taken orally two times a day, without food (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Table 5**). Tablets should be swallowed whole.

Missed Dose

If a dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, no additional dose should be taken and the regular dosing schedule should be resumed.

No more than two doses of ZAXINE (1 tablet twice a day) should be taken in a 24-hour period.

OVERDOSAGE

No specific information is available on the treatment of overdosage with ZAXINE (rifaximin). In clinical studies at doses higher than the recommended dose (i.e., > 1100 mg/day [up to a daily maximum of 2400 mg rifaximin]), adverse reactions were similar in subjects receiving ZAXINE or placebo. In the case of overdosage, discontinue ZAXINE, treat symptomatically, and institute supportive measures as required.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Rifaximin is a non-aminoglycoside semi-synthetic antibacterial derived from rifamycin SV. Rifaximin acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis. Rifaximin has a broad antimicrobial spectrum against many Gram-positive, Gram-negative, aerobic and anaerobic bacteria, including ammonia-producing species. Rifaximin may inhibit the division of urea-deaminating bacteria, thereby reducing the production of ammonia and other compounds that are believed to be important in the pathogenesis of hepatic encephalopathy.

Due to the generally low absorption from the gastro-intestinal tract, rifaximin is locally-acting in the intestinal lumen and clinically not effective against invasive pathogens.

Pharmacokinetics

Absorption:

After a single dose and multiple doses of ZAXINE (rifaximin) 550 mg in healthy subjects, the mean time to reach peak plasma concentrations was about an hour. The pharmacokinetic (PK) parameters were highly variable and the accumulation ratio based on AUC was 1.37.

The PK of ZAXINE in patients with a history of HE was evaluated after administration of ZAXINE, 550 mg two times a day. The PK parameters were associated with a high variability and mean ZAXINE exposure (AUC_{tau}) in patients with a history of HE (147 ng•h/mL) was approximately 12-fold higher than that observed in healthy subjects following the same dosing

regimen (12.3 ng•h/mL). When PK parameters were analyzed based on Child-Pugh Class A, B, and C, the mean AUCτ was 10-, 13-, and 20-fold higher, respectively, compared to that in healthy subjects (Table 4).

Table 4 Mean (± SD) Pharmacokinetic Parameters of ZAXINE at Steady-State in Patients with a History of Hepatic Encephalopathy by Child-Pugh Class[1]

	Healthy Subjects (n=14)	Child-Pugh Class		
		A (n=18)	B (n=15)	C (n=6)
AUC_{tau} (ng•h/mL)	12.3 ± 4.8	118 ± 67.8	169 ± 55.7	257 ± 100
C_{max} (ng/mL)	3.4 ± 1.6	19.5 ± 11.4	25.4 ± 11.9	39.7 ± 13.5
T_{max}[2] (h), range	0.8 (0.5, 4.0)	1 (0.9, 10)	1 (0.97, 4.2)	1 (0, 2)
$T_{½}$ (h)	4.2 ± 3.3	8.1 ± 3.6	8.0 ± 2.5	6.4 ± 1.1

[1] Cross-study comparison with PK parameters in healthy subjects
[2] Median

Food Effect in Healthy Subjects

A high-fat meal consumed 30 minutes prior to ZAXINE dosing in healthy subjects delayed the mean time to peak plasma concentration from 0.75 to 1.5 hours and increased the systemic exposure (AUC) of ZAXINE by 2-fold (Table 5).

Table 5 Mean (± SD) Pharmacokinetic Parameters After Single-Dose Administration of Rifaximin 550 mg in Healthy Subjects Under Fasting and Fed Conditions (N=12)

Rifaximin Parameters	Fasting	Fed
C_{max} (ng/mL)	4.0 ± 1.5	4.8 ± 4.3
T_{max} (h)[a]	0.8 (0.5, 2.1)	1.5 (0.5, 4.1)
$t_{½}$ (h)	1.8 ± 1.4	4.8 ± 1.3
$AUC_{0-\infty}$ (ng*h/mL)	11.1 ± 4.2	22.5 ± 12

[a]Median and range

Distribution:

Rifaximin is moderately bound to human plasma proteins. *In vivo*, the mean protein binding ratio was 67.5% in healthy subjects and 62% in patients with hepatic impairment when ZAXINE 550 mg was administered.

Metabolism and Excretion:

In vitro studies in human liver cell lines suggested that rifaximin is metabolized by CYP3A4. (See **DETAILED PHARMACOLOGY, *HUMAN PHARMACOLOGY***.)

Rifaximin is almost exclusively excreted in faeces. In a mass balance study, after administration of 400 mg ^{14}C-rifaximin orally to healthy subjects, of the 96.94% total recovery, 96.62% of the administered radioactivity was recovered in faeces almost exclusively as the unchanged drug and 0.32% was recovered in urine mostly as metabolites with 0.03% as the unchanged drug. This suggests that the absorbed rifaximin undergoes metabolism with minimal renal excretion of the unchanged drug. Rifaximin was detected in the bile after cholecystectomy in patients with intact

gastrointestinal mucosa, indicating some biliary excretion of systemically absorbed rifaximin.

Special Populations and Conditions

Hepatic Insufficiency: The systemic exposure of rifaximin was elevated in patients with hepatic impairment compared to healthy subjects. When PK parameters were analyzed based on Child-Pugh Class A, B, and C, the mean AUCτ was 10-, 13-, and 20-fold higher, respectively, compared to that in healthy subjects. (See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Table 4**.)

Renal Insufficiency: The pharmacokinetics of rifaximin in patients with impaired renal function have not been studied.

STORAGE AND STABILITY

Store ZAXINE (rifaximin) tablets at 20–25°C (68–77°F); excursions permitted to 15–30°C (59-86°F). Store in a tightly closed container away from hear and direct light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

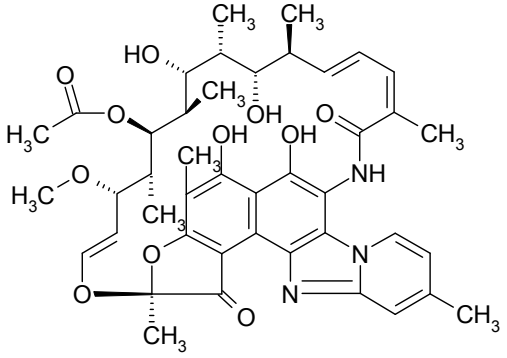
ZAXINE (rifaximin) 550 mg is a pink, oval, biconvex tablet with “rfx” debossed on one side. It is available in bottles of 60 tablets.

Non-medicinal ingredients: colloidal silicon dioxide, glyceryl distearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Rifaximin
Chemical name:	(2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca-[1,11,13]trienimino)benzofuro[4,5-e]pyrido[1,2-α]-benzimidazole-1,15(2*H*)-dione,25-acetate
Molecular formula and molecular mass:	$C_{43}H_{51}N_3O_{11}$ MW=785.9
Structural formula:	

Physicochemical properties: Rifaximin is red/orange microcrystalline powder, soluble in methanol, chloroform, acetone and ethyl acetate. It is practically insoluble in water. It has a pK_a of 6.77. The partition co-efficient (*n*-octanol-water) is 2.76.

CLINICAL TRIALS

The safety and efficacy of ZAXINE (rifaximin) 550 mg twice daily in adult patients in remission from overt HE was assessed in one randomized double-blind, parallel group, controlled multicentre six month trial, and in one multicentre, open-label, long term study.
Study demographics and trial design are summarized in Table 6.

Table 6 Summary of patient demographics for clinical trials in prevention of overt HE recurrence in patients ≥18 years of age

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N = number)	Mean age (Range)	Gender
RFHE3001 (Pivotal - Safety and Efficacy)	Randomized placebo controlled, double-blind, multicentre (US, Canada, Russia)	550 mg BID, oral, up to 6 months Placebo BID, up to 6 months	N = 299 Rifaximin =140 Placebo = 159	56 years (21-82 years)	61% male
RFHE3002 (Safety)	Open-label, multicentre (US, Canada, Russia), treatment extension study	550 mg BID, oral at least 24 months	N = 322 rifaximin subjects (152 from study 3001 [70 rifaximin and 82 placebo] and 170 new subjects)	57 years (21-82 years)	61 % male

More than 90% of the subjects in both studies received concomitant lactulose. No patients were enrolled with a MELD score >25.

Study Results RFHE3001:

The primary efficacy endpoint was the time to first breakthrough overt HE episode. Patients were withdrawn after a breakthrough overt HE episode.

Breakthrough overt HE episodes were experienced by 31 of 140 subjects (22%) in the ZAXINE group and by 73 of 159 subjects (46%) in the placebo group during the 6-month treatment period. ZAXINE significantly reduced the risk of overt HE breakthrough by 58% ($p<0.0001$) during the 6-month treatment period.

A key secondary endpoint included time to first HE-related hospitalization. HE-related hospitalizations (hospitalizations directly resulting from HE, or hospitalizations complicated by HE) were reported for 19 of 140 subjects (14%) and 36 of 159 subjects (23%) in the ZAXINE and placebo groups, respectively. ZAXINE significantly reduced the risk of overt HE-related hospitalizations by 50% ($p<0.0129$) during the 6-month treatment period.

Study Results RFHE3002:

In this open-label, uncontrolled study, treatment with ZAXINE for periods up to 24 months did not result in any loss of effect regarding protection from breakthrough overt HE episodes and the reduction in the burden of hospitalization. The time to first breakthrough overt HE episode profiles demonstrated long-term maintenance of remission in new ZAXINE subjects in RFHE3002 (including placebo crossover subjects from RFHE3001) and continuing ZAXINE subjects in RFHE3002 (i.e., ZAXINE rollover subjects from RFHE3001).

DETAILED PHARMACOLOGY

ZAXINE (rifaximin) contains rifaximin-α, one of the polymorphic forms of rifaximin.

Mechanism of Action

See **ACTION AND CLINICAL PHARMACOLOGY**.

ANIMAL PHARMACOLOGY

Pharmacodynamics

The safety pharmacology, neurobehavioral, gastrointestinal, renal, cardiovascular, and neurological effects, were evaluated in mice, rats, cats, and dogs following single oral or intraduodenal doses ranging from 100 to 1000 mg/kg. In mice, rifaximin did not show significant pharmacologic effects on neurobehavior, locomotion, motor coordination, gastrointestinal motility, proconvulsant activity, hexobarbital-induced sleep time, and diazepam-inhibited seizure activity. No significant effects were seen on gastric acid secretion, gastric mucosa, or urinary volume and electrolyte excretion in rats. Rifaximin did not demonstrate significant effects on hemodynamics and respiration in dogs, rats or guinea pigs, or autonomic function in cats. Thus, from the safety pharmacology studies, the no effect level was 1000 mg/kg. This dose level is about 62.5 fold greater than the therapeutic dose, given that the daily maximum clinical dose is anticipated to be 1100 mg/d which is equivalent to 15.7 mg/kg for a 70 kg subject and 647 mg/m^2 for a patient with 1.7 m^2 body surface area.

Pharmacokinetics

Following oral administration of ^{14}C-rifaximin, the drug is poorly absorbed. Most of the radioactivity was demonstrated in the gastrointestinal tract. Systemic availability of orally administered ^{14}C-rifaximin (24 mg/kg) was not more than 2-5% of the oral dose in rats or 0.5% of the oral dose in dogs. In rats, the majority of drug activity >96% was demonstrated in faeces, 0.6% in the liver and 0.01% in the kidney. Biliary excretion approximates 0.5% to 1.7% of the oral dose, suggesting that there is a significant first pass removal of rifaximin by the liver, for the small proportion of the oral dose absorbed. In dogs administered with 2.4 mg/kg IV ^{14}C-rifaximin, the majority of the dose was recovered from faeces (83-93 %) while 0.45% from urine suggesting the faecal radioactivity from IV dose is probably initially excreted in bile. Effect of rifaximin on hepatic and intestinal drug metabolizing enzymes was evaluated *ex vivo* in CD rats. Following 50-300 mg/kg/day administration of rifaximin orally for 26 weeks in rats, rifaximin did not demonstrate significant induction potential in liver/GI tract.

In Vitro Study

In vitro interspecies comparison of metabolism of rifaximin in rat, rabbit, dog and human hepatocytes demonstrated that the rate of metabolism varied and was greatest for rabbit, followed by dog, rat and human. Large interspecies differences were reported in major metabolites formed. Different major metabolites were observed for each species. The major human metabolite (25-desacetyl rifaximin) was not detected in rat and was demonstrated as a minor metabolite in rabbits and dogs.

HUMAN PHARMACOLOGY

***In Vitro* Studies**

QT/QTc Prolongation
In vitro rifaximin concentrations of ≥ 30 μM (23,577 ng/mL) demonstrated a statistically significant increase in inhibition of the hERG channel; the IC_{50} was estimated to be > 100 μM (78590 ng/mL).

Pharmacokinetics
Rifaximin is metabolized by CYP3A4. Multiple rifaximin metabolism pathways were identified, including deacetylation, demethylation, mono-oxidation, and desaturation. The major metabolite observed was 25-desacetyl rifaximin. Rifaximin has low potential to induce CYP3A4 enzyme activity (at a concentration of 0.2 μM [157 ng/ml]). Rifaximin did not inhibit cytochrome P450 isozymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 at concentrations up to 200 ng/ml. However, at higher concentrations rifaximin inhibited CYP 3 A4 (IC_{50} = 25 μM, [19,648 ng/ml] equivalent to 900x the clinical unbound Cmax in hepatically impaired patients). Rifaximin is a substrate and a weak inhibitor of P-glycoprotein (P-gp). Rifaximin partly inhibited digoxin transport at 50 μM (39,316 ng/ml) through Caco-2 monolayers.

MICROBIOLOGY

Spectrum of Activity
Rifaximin has a broad antimicrobial spectrum.

Development of Resistance
Rifaximin is a structural analog of rifampin. Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied.

Escherichia coli has been shown to develop resistance to rifaximin *in vitro*. However, the clinical significance of such an effect has not been studied.

TOXICOLOGY
Following single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity studies were conducted to investigate the toxicity of rifaximin:

Single-dose
Single oral doses of up to 2000 mg/kg rifaximin were nontoxic to mice and rats.

Repeat Dose
Oral administration of rifaximin for 3-6 months produced hepatic proliferation of connective tissue in rats (50 mg/kg/day) and fatty degeneration of liver in dogs (100 mg/kg/day). However,

plasma drug levels were not measured in these studies. Rifaximin was studied at doses as high as 300 mg/kg/day in rats for 6 months and 1000 mg/kg/day in dogs for 9 months, and no signs of hepatotoxicity were observed. The maximum plasma $AUC_{0\text{-}8\ hr}$ values from the 6 month rat and 9 month dog toxicity studies (range: 42-127 ng•h/mL) was lower than the maximum plasma $AUC_{0\text{-}8hr}$ values in cirrhotic patients (range: 19-306 ng•h/mL).

Repeat oral administration of rifaximin at 1000 mg/kg/d for 39 weeks was nontoxic to the dog. To achieve higher exposures to rifaximin, dogs were given 1000 mg/kg/d of the amorphous form of rifaximin by the oral route. The rate and extent of systemic exposure to rifaximin amorphous form was approximately 90-fold higher than for those administered rifaximin alpha. At week 26, except for orange-colored feces/fur and non-specific stress-induced thymic atrophy/involution, no consistent clinical pathologic or histopathologic changes attributable to rifaximin amorphous were observed in these dogs.

Genotoxicity

Rifaximin did not show evidence of mutagenic activity in a standard battery that included bacterial and yeast gene mutation assays, mammalian CHO/HGPRT gene mutation assay, chromosomal aberration assay with human lymphocytes, and *in vivo* tests e.g., rat bone marrow micronucleus assay. Rifaximin does not induce unscheduled DNA synthesis in primary rat hepatocytes and unscheduled DNA synthesis in rat hepatocytes after *in vivo* treatment.

Carcinogenicity

Malignant schwannomas in the heart were significantly increased in male Crl: CD rats that received rifaximin by oral gavage for two years at 150 to 250 mg/kg/day (doses equivalent to 1.3 to 2.2 times the recommended dose, based on relative body surface area comparisons). There was no increase in tumors in Tg.rasH2 mice dosed orally with rifaximin for 26 weeks at 150 to 2000 mg/kg/day (doses equivalent to 0.7 to 9 times the recommended daily dose based on relative body surface area comparisons).

Reproductive Toxicity and Fertility

In a rat embryo-fetal development study, a slight and transient delay in ossification that did not affect the normal development of the offspring, was observed at 300 mg/kg/day (equivalent to 2.6 times the clinical dose for hepatic encephalopathy, adjusted for body surface area). In the rabbit, following oral administration of rifaximin during gestation, an increase in the incidence of skeletal variations was observed (at doses similar to clinical dose). The clinical relevance of these findings is not known. In another study in the rabbit following to administration of rifaximin 62.5- 1000 mg/kg/d orally for 14 days in pregnant rabbits from gestation Day 6 – 19 rifaximin tissue concentrations in the fetal and adult brain and liver, and in the placenta were evaluated. In pregnant rabbits treated with rifaximin 250 and 1000 mg/kg/d minimal rifaximin exposure to fetus was demonstrated.

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PART III: CONSUMER INFORMATION

PrZAXINE

(rifaximin)

This leaflet is part III of a three-part "Product Monograph" published when ZAXINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZAXINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ZAXINE is an antibiotic that acts on the bacteria in the gastrointestinal tract. ZAXINE is used to help prevent recurring episodes of a condition called **hepatic encephalopathy (HE)**. It may be used in conjunction with lactulose, as directed by your doctor. HE occurs when the liver is not working properly and cannot remove toxins from the blood which affect brain function.

ZAXINE is intended to be used for preventing HE only in those adult patients where HE is likely to occur again.

What it does:

ZAXINE is thought to work by reducing the production of toxins released into the blood by bacteria in the gut.

When it should not be used:

If you are allergic (hypersensitive) to the active substance rifaximin, rifamycin antibacterial agents, or any of the other ingredients of ZAXINE (see **What the nonmedicinal ingredients are**).

What the medicinal ingredient is:

The active substance is rifaximin. Each tablet contains 550 mg rifaximin.

What the nonmedicinal ingredients are:

colloidal silicon dioxide, glyceryl distearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.

What dosage forms it comes in:

Tablets: 550 mg

WARNINGS AND PRECAUTIONS

BEFORE you use ZAXINE talk to your doctor or pharmacist if:

- You have severe liver problems – there is an increase in systemic (blood) exposure to rifaximin in subjects with severe liver disease.
- You have any allergies to this drug or its ingredients
- You are pregnant or think you may be pregnant, ask your doctor or pharmacist for advice before taking this medicine. Your doctor can discuss with you the risks and benefits involved.
- You are breastfeeding ask your doctor or pharmacist for advice before taking this medicine. It is not known whether rifaximin passes into breast milk.
- ZAXINE should not be used in children or adolescents less than 18 years of age, as there is no information on the use in that population.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are using, have recently used, or might use any other medicines, including non-prescription or herbal medicines. Tell your doctor if you are taking warfarin or oral contraceptives.

PROPER USE OF THIS MEDICATION

Usual adult dose:

The recommended dosage of ZAXINE tablets is one tablet twice daily. ZAXINE should be taken without food. Tablets should be swallowed whole with plenty of water. Do not crush tablets.

Overdose:

In case of drug overdose, contact a health professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, it should be taken as soon as possible. However, if it is almost time for the next dose, no additional dose should be taken and the regular dosing schedule should be resumed.

No more than two doses of ZAXINE (1 tablet twice a day) should be taken in a 24-hour period.

If you have trouble remembering to take your medicine, ask your pharmacist for some hints.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, this medicine can cause side effects, although not everybody gets them. The most common side effects reported with ZAXINE are:

- Diarrhea
- Nausea
- Abdominal pain or bloating
- Muscle spasms
- Dizziness or unsteadiness
- Headache
- Itchiness

If you experience symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness, you may have *Clostridium difficile* colitis (bowel inflammation). If this occurs, stop taking Zaxine and contact your doctor immediately.

In rare cases, allergic and skin reactions such as: hives; rash (with or without blisters); swelling of face, lips, tongue, or throat;

difficult or painful swallowing; trouble breathing have occurred. Contact your doctor immediately if these allergic reactions occur.

Despite generally limited absorption of this drug from the gastrointestinal tract into the body, like all rifamycin derivatives, rifaximin may cause a reddish discolouration of the urine, tears and sweat.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

This is not a complete list of side effects. For any unexpected effects while taking ZAXINE, contact your doctor or pharmacist.

HOW TO STORE IT

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle, after "Exp:". The expiry date refers to the last day of that month.

ZAXINE should be stored at room temperature (15° to 30°C) in a tightly closed container away from heat and direct light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at: www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.website.document

or by contacting the sponsor, Salix Pharmaceuticals, Inc., at: 1-800-508-0024
This leaflet was prepared by Salix Pharmaceuticals, Inc.

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