Dear Healthcare Professional,

At MPR we strive to bring you important drug information in a concise and timely fashion. In keeping with this goal, we are pleased to bring you this PRESCRIBING ALERT about XIFAXAN (rifaximin) 550 mg tablets from Salix Pharmaceuticals, Inc.

XIFAXAN 550 mg is FDA approved for the reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients 18 years and older. Recurrent episodes of HE may lead to long-term cognitive dysfunction, which may be irreversible in patients with a history of overt HE. In a pivotal clinical trial, XIFAXAN 550 mg demonstrated its ability to reduce the risk of overt HE recurrence over a 6-month period and reduce HE-related hospitalization.

More information regarding the use of XIFAXAN 550 mg is available in the current edition of MPR.

For your reference, please see the complete Prescribing Information for XIFAXAN 550 mg.

Sincerely,

Grace L. McBride
Editorial Director
MPR Custom Programs

REFERENCES

IMPORTANT SAFETY INFORMATION
XIFAXAN 550 mg is indicated for reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥18 years of age. In the trials of XIFAXAN for HE, 91% of the patients were using lactulose concomitantly. XIFAXAN has not been studied in patients with MELD scores >25, and only 8.6% of patients in the controlled trial had MELD scores over 19. There is increased systemic exposure in patients with more severe hepatic dysfunction. Therefore, caution should be exercised when administering XIFAXAN to patients with severe hepatic impairment (Child-Pugh C).

XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, 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. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued.

The most common adverse reactions occurring in >8% of patients in the clinical study were edema peripheral (15%), nausea (14%), dizziness (13%), fatigue (12%), ascites (11%), muscle spasms (9%), pruritus (9%), and abdominal pain (9%).

Xifaxan550 is not available for sale outside the U.S.

Xifaxan550 is licensed by Alfa Wassermann S.p.A. to Salix Pharmaceuticals, Inc.
Shown to reduce risk of overt hepatic encephalopathy recurrence

XIFAXAN 550
(rifaximin) 550 mg tablets

>25; only 8.6% of patients in the controlled trial had MELD >19. Increased systemic exposure in patients with more severe hepatic dysfunction; caution should be exercised in patients with severe hepatic impairment (Child-Pugh C). Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN; may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected/confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued.

Interactions: See full Prescribing Information.

Adverse Reactions:
(≥10%): Peripheral edema, nausea, dizziness, fatigue, ascites.

How Supplied:
Tablets: 550 mg—60 count bottle

Company: Salix Pharmaceuticals, Inc.
Pharmacologic Class: Rifamycin derivative
Active Ingredients: Rifaximin 550 mg tablets.
Indications: Reduce the risk of overt hepatic encephalopathy (OHE) recurrence in patients 18 years and older.
Adults: 550 mg 2 times daily.
Precautions: Not studied in patients with MELD scores >25; only 8.6% of patients in the controlled trial had MELD >19. Increased systemic exposure in patients with more severe hepatic dysfunction; caution should be exercised in patients with severe hepatic impairment (Child-Pugh C). Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN; may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected/confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued.

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Overt hepatic encephalopathy (OHE) is a chronic condition
- OHE is a chronically debilitating complication of cirrhosis
- Prevention of OHE episodes is an important goal in the treatment of patients with liver disease

Long-term cognitive impairment may occur due to recurrent overt HE
- A clinical study showed that cirrhotic patients with OHE (n=54) had more cognitive dysfunction than normal cirrhotic patients (n=52) despite treatment with lactulose (Figure 1)
  - Patients with OHE performed significantly worse on a battery of psychometric tests (P<0.001) and were unable to demonstrate a capacity for learning

Figure 1

DIFFERENCE IN THE INCIDENCE OF LEARNING DEFICITS

Comparison of cirrhotic patients with and without overt hepatic encephalopathy experiencing learning deficits

74% P=0.0001

7%

Cirrhotic patients with overt HE

Normal cirrhotic patients

All patients were controlled on lactulose therapy

*This study evaluated the cognitive function of cirrhotic patients using psychometric tests and the inhibitory control test (ICT). Outcomes were used to determine learning of response inhibition. Two cross-sectional studies (A and B) compared data from stable cirrhotic patients with or without prior OHE. Study A included 226 cirrhotic patients, and study B included 50 additional patients who developed ≥1 documented OHE episodes during follow-up. A prospective analysis assessed the cognitive performance of 79 patients in a psychometric evaluation. Of the 59 patients who returned for a retest, 15 had developed OHE and were treated with lactulose for 36 ± 25 days before another test. OHE = overt hepatic encephalopathy.

Source: Bajaj 2010.
XIFAXAN 550 mg reduced HE-related hospitalizations over 6 months\(^1,3\) (Figure 2)

**REDUCED HEPATIC ENCEPHALOPATHY-RELATED HOSPITALIZATIONS**

![Graph showing probability of HE-related hospitalizations over 6 months](image)

\(1\) HE-related hospitalization defined as hospitalization directly caused by HE or a hospitalization during which an HE event occurred.\(^1\)

\(^1\) In a randomized, placebo-controlled, double-blind, multicenter, multinational, 6-month study, the efficacy of XIFAXAN 550 mg (taken orally 2 times a day) was evaluated in 299 adult subjects. Inclusion criteria: currently in remission (Conn score of 0 or 1) from HE and \(\geq 2\) episodes of HE associated with chronic liver disease in the previous 6 months. The key secondary end point was the time to the first hospitalization involving HE.\(^1,3\)

\(^3\) Lactulose was used concomitantly by 91% of patients in both arms (average daily dose of 3.3 cups/day [15 mL/cup]).\(^1\)

Sources: Bass 2010\(^1\); XIFAXAN [prescribing information]\(^3\); Data on file.\(^4\)

XIFAXAN 550 mg reduced the risk of overt HE recurrence over a 6-month period\(^3\) (Figure 3)

**EFFICACY IN DECREASING OVERT HEPATIC ENCEPHALOPATHY RECURRENCE**

![Graph showing probability of breakthrough overt HE episodes over 6 months](image)

\(^3\) In a randomized, placebo-controlled, double-blind, multicenter, multinational, 6-month study, the efficacy of XIFAXAN 550 mg (taken orally 2 times a day) was evaluated in 299 adult subjects. Inclusion criteria: currently in remission (Conn score of 0 or 1) from HE and \(\geq 2\) episodes of HE associated with chronic liver disease in the previous 6 months. The primary end point was the time to first breakthrough HE episode, defined as a marked deterioration in neurological function (an increase in Conn score to Grade \(\geq 2\) or an increase in Conn score and asterixis grade of 1 each if subject entered study at Grade 0).\(^1,3\)

\(^3\) Lactulose was used concomitantly by 91% of patients in both arms (average daily dose of 3.3 cups/day [15 mL/cup]).\(^1\)

Sources: Bass 2010\(^1\); XIFAXAN [prescribing information]\(^3\); Data on file.\(^4\)

Please see Important Safety Information and complete Prescribing Information.

(continued on next page)
Offers favorable safety and tolerability profile when used as directed

- Incidence of adverse reactions with nonsystemic XIFAXAN 550 mg was comparable to placebo\(^3,4\) (Figure 4)

Figure 4

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Xifaxan 550 mg (n=140) (91% concomitant lactulose)</th>
<th>Placebo (n=159) (91% concomitant lactulose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Serious event</td>
<td>36%</td>
<td>40%</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>15%</td>
<td>8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13%</td>
<td>8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Ascites</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Anemia</td>
<td>8%</td>
<td>4%</td>
</tr>
</tbody>
</table>

\(^*\)Most common adverse reactions occurring in ≥8% of patients taking XIFAXAN 550 mg. Sources: XIFAXAN [prescribing information]\(^3\); Data on file.\(^4\)

XIFAXAN 550 mg has not been shown to cause clinically relevant resistance when used as directed\(^5,6\)

The HE Living Program offers patients, caregivers, and healthcare professionals (HCPs) ongoing treatment support for overt HE management

- Adults ≥18 years of age with OHE are eligible to participate in the HE Living Program
- Reimbursement support is part of the HE Living Program
  - You or your staff can call the XIFAXAN Reimbursement Helpline at 1-866-XIFAXAN (1-866-943-2926) to get answers to third-party coverage questions and for timely solutions to issues you encounter before or after submitting a patient’s claim
  - The XIFAXAN Reimbursement Helpline can negotiate appeals on behalf of patients, should their claims be denied
- Financial support is part of the HE Living Program
  - $100 co-pay card is available for eligible patients to use each month
  - Patients on Medicare will also receive financial support from drug manufacturers under the Part D plan
  - According to the plan, Salix will pay 50% of the cost of XIFAXAN 550 mg while a patient is in the “donut hole” (gap in coverage)

Please see Important Safety Information and complete Prescribing Information.
Ongoing treatment is part of the HE Living Program

- The 24-hour call center (1-866-XIFAXAN [1-866-943-2926]) is available to answer patients’ or caregivers’ questions
- Compliance calls with associated prescription and appointment reminders help patients stay on therapy
- Patient education brochures contain information about disease education, the importance of staying on therapy to avoid an overt HE episode, and what to expect from treatment with XIFAXAN 550 mg

Enrolling patients in the HE Living Program is easy

- HCPs, patients, or caregivers can enroll in the HE Living Program by visiting www.helpenroll.com or by calling 1-866-XIFAXAN (1-866-943-2926)

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REFERENCES


RIFHE 11/74
10/11