

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ALOSETRON hydrochloride tablets, for oral use.
Initial U.S. Approval: 2000

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

Inrequent but serious gastrointestinal adverse reactions have been reported with the use of aloe setron hydrochloride. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization and, rarely, blood transfusion, surgery, and death.

- Alosetron hydrochloride is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy. (1)
- Discontinue aloe setron hydrochloride immediately in patients who develop constipation or symptoms of ischemic colitis. Do not resume aloe setron hydrochloride in patients who develop ischemic colitis. (2.1, 5.1, 5.2)

RECENT MAJOR CHANGES

Contraindications, Lack of Understanding of Patient Acknowledgement Form (4.3) Removed 01/2016
Warnings and Precautions, Prescribing Program for Alosetron Hydrochloride (5.3) Removed 01/2016

INDICATIONS AND USAGE

Alosetron Hydrochloride Tablets are a selective serotonin 5-HT_{2A} antagonist indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have:

- chronic IBS symptoms (generally lasting 6 months or longer),
- had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and
- not responded adequately to conventional therapy. (1)

Severe IBS includes diarrhea and 1 or more of the following:

- frequent and severe abdominal pain/discomfort,
- frequent bowel urgency or fecal incontinence,
- disability or restriction of daily activities due to IBS. (1)

DOSE AND ADMINISTRATION

- Starting dose is 0.5 mg twice a day (2.1)
- May increase dose to 1 mg twice a day after 4 weeks if starting dosage is well tolerated but does not adequately control IBS symptoms (2.1)
- Discontinue aloe setron hydrochloride tablets in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice a day. (2.1)

DOSE FORMS AND STRENGTHS

Tablets: 0.5 and 1 mg (3)

CONTRAINDICATIONS

- Do not initiate in patients with constipation (4.1)
- History of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions; ischemic colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn's disease or ulcerative colitis; diverticulitis; severe hepatic impairment (4.2)
- Concomitant use of fluvoxamine (4.3)

WARNINGS AND PRECAUTIONS

- Serious Complications of Constipation: May occur in some patients without warning. Include obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia and in rare cases perforation and death have been reported. Risk is increased in patients who are elderly, debilitated, or taking medications that decrease bowel motility. (5.1)
- Discontinue aloe setron hydrochloride immediately if constipation occurs. (5.1)
- Ischemic colitis: May occur in some patients without warning. Promptly evaluate patients with signs of ischemic colitis (e.g., rectal bleeding, bloody diarrhea, new or worsening abdominal pain). (5.2)
- Discontinue aloe setron hydrochloride immediately if signs of ischemic colitis occur, such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥2% and >-placebo) in clinical studies were constipation, abdominal discomfort and pain, nausea, and gastrointestinal discomfort and pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP1A2 inhibitors: Avoid concomitant uses because of increased exposure and half-life of aloe setron. Use with fluvoxamine is contraindicated. (4.3, 7.1)
- CYP3A4 inhibitors: Use with caution in combination due to increased exposure of aloe setron. (7.2)

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Contraindicated in severe hepatic impairment. Use with caution in patients with mild or moderate hepatic impairment. (4.2, 8.6)
- Geriatric use: Elderly patients may be at greater risk for complications of constipation. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Issued: 08/2017

Medication Guide

Alosetron Hydrochloride Tablets (a-LOE-se-iron HYE-droe-KLOR-ide)

Before using aloe setron hydrochloride tablets for the first time, you should:

- Understand that aloe setron hydrochloride tablets have serious risks for some people.
- Read and follow the directions in this Medication Guide.

Carefully read the medication guide you get with each refill for aloe setron hydrochloride tablets. There may be new information. This medication guide does not take the place of talking with your doctor.

1. What is the most important information I should know about aloe setron hydrochloride tablets?

A. Alosetron hydrochloride tablets are a medicine only for some women with severe chronic irritable bowel syndrome (IBS) whose:

- main problem is diarrhea and
- IBS symptoms have not been helped enough by other treatments.

B. Some patients have developed serious bowel side effects while taking aloe setron hydrochloride tablets. Serious bowel (intestine) side effects can happen suddenly, including the following.

1. **Serious complications of constipation:** About 1 out of every 1,000 women who take aloe setron hydrochloride tablets may get serious complications of constipation. These complications **may lead to a hospital stay and, in rare cases, blood transfusions, surgery, and death.** People who are older, who are weak from illness, or who take other constipating medicines may be more likely to have serious complications of constipation with aloe setron hydrochloride tablets.

To lower your chances of getting serious complications of constipation, do the following:

- **If you are constipated,** do not start taking aloe setron hydrochloride tablets.
- **If you get constipated while taking aloe setron hydrochloride tablets,** stop taking them right away and call your doctor.
- **If your constipation does not get better after stopping aloe setron hydrochloride tablets,** call your doctor again.
- **If you stopped taking aloe setron hydrochloride tablets,** do not start taking aloe setron hydrochloride tablets again unless your doctor tells you to do so.

2. **Ischemic colitis (reduced blood flow to the bowel):** About 3 out of every 1,000 women who take aloe setron hydrochloride tablets over a 6-month period may get a serious problem where blood flow to parts of the large bowel is reduced. This is called ischemic colitis. The chance of getting ischemic colitis when you take aloe setron hydrochloride tablets for more than 6 months is not known. **Ischemic colitis may lead to a hospital stay and, in rare cases, blood transfusions, surgery, and death.** **To lower your chances of getting serious complications of ischemic colitis, stop taking aloe setron hydrochloride tablets and call your doctor right away if you get:**

- new or worse pain in your stomach area (abdomen) or
- blood in your bowel movements.

C. Are aloe setron hydrochloride tablets right for you?

Alosetron hydrochloride tablets may be right for you if all of these things are true about you:

- Your doctor has told you that your symptoms are due to IBS.
- Your IBS bowel problem is diarrhea.
- Your IBS has lasted for 6 months or longer.
- You tried other IBS treatments and they did not give you the relief you need.
- Your IBS is severe.

You can tell if your IBS is severe if **at least 1** of the following is true for you:

- You have lots of painful stomach cramps or bloating.
- You often cannot control the need to have a bowel movement, or you have “accidents” where your underwear gets dirty from diarrhea or bowel movements.
- You cannot lead a normal home or work life because you need to be near a bathroom.

Enough testing has not been done to confirm if aloe setron hydrochloride tablets works in men or children under age 18.

2. What are aloe setron hydrochloride tablets?

Alosetron hydrochloride tablets are a medicine only for some women with severe chronic IBS whose:

- main problem is diarrhea and
- IBS symptoms have not been helped enough by other treatments.

Alosetron hydrochloride tablets do not cure IBS, and it may not help every person who takes it. For those who are helped, aloe setron hydrochloride tablets reduce lower stomach area (abdominal) pain and discomfort, the sudden need to have a bowel movement (bowel urgency), and diarrhea from IBS. If you stop taking aloe setron hydrochloride tablets, your IBS symptoms may return within 1 or 2 weeks to what they were before you started taking aloe setron hydrochloride tablets.

Alosetron hydrochloride tablets are not recommended for children.

3. Who should not take aloe setron hydrochloride tablets?

Alosetron hydrochloride tablets are not right for everyone. **Do not take aloe setron hydrochloride tablets if any of the following apply to you:**

- Your main IBS problem is constipation or you are constipated most of the time.
- You have had a serious problem from constipation. **If you are constipated now, do not start taking aloe setron hydrochloride tablets.**
- You have had serious bowel blockages.
- You have had blood flow problems to your bowels, such as ischemic colitis.
- You have had blood clots.
- You have had Crohn's disease, ulcerative colitis, diverticulitis, or severe liver disease.
- You do not understand this Medication Guide or you are not willing to follow it.
- You are taking fluvoxamine (LUVOX®).

4. What should I talk about with my doctor before taking aloe setron hydrochloride tablets?

Talk with your doctor:

- about the possible benefits and risks of aloe setron hydrochloride tablets.
- about how much of a problem IBS is in your life and what treatments you have tried.
- about any other illnesses you have and medicines you take or plan to take. These include prescription and non-prescription medicines, supplements, and herbal remedies. Certain illnesses and medicines can increase your chance of getting serious side effects while taking aloe setron hydrochloride tablets. Other medicines may interact with how the body handles aloe setron hydrochloride tablets.

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Adult Patients
- 2.2 Patients With Hepatic Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Constipation
- 4.2 History of Severe Bowel or Hepatic Disorders
- 4.3 Concomitant Use of Fluvoxamine

5 WARNINGS AND PRECAUTIONS

- 5.1 Serious Complications of Constipation
- 5.2 Ischemic Colitis

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 CYP1A2 Inhibitors
- 7.2 CYP3A4 Inhibitors
- 7.3 Other CYP Enzymes

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

Inrequent but serious gastrointestinal adverse reactions have been reported with the use of aloe setron hydrochloride. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization, and rarely, blood transfusion, surgery, and death.

- Alosetron hydrochloride is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy *[see Indications and Usage (1)]*.
- Alosetron hydrochloride should be discontinued immediately in patients who develop constipation or symptoms of ischemic colitis. Patients should immediately report constipation or symptoms of ischemic colitis to their prescriber. Alosetron hydrochloride should not be resumed in patients who develop ischemic colitis. Patients who have constipation should immediately contact their prescriber if the constipation does not resolve after aloe setron hydrochloride is discontinued. Patients with resolved constipation should resume aloe setron hydrochloride only on the advice of their treating prescriber *[see Dosage and Administration (2.1), Warnings and Precautions (5.1), (5.2)]*.

1 INDICATIONS AND USAGE

Alosetron hydrochloride tablets are indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have:

- chronic IBS symptoms (generally lasting 6 months or longer),
- had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and
- not responded adequately to conventional therapy.

Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following:

- frequent and severe abdominal pain/discomfort,
- frequent bowel urgency or fecal incontinence,
- disability or restriction of daily activities due to IBS.

Because of inrequent but serious gastrointestinal adverse reactions associated with aloe setron hydrochloride tablets, the indication is restricted to those patients for whom the benefit-to-risk balance is most favorable.

Clinical studies have not been performed to adequately confirm the benefits of aloe setron hydrochloride tablets in men.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Patients

To lower the risk of constipation, aloe setron hydrochloride tablets should be started at a dosage of 0.5 mg twice a day. Patients who become constipated at this dosage should stop taking aloe setron hydrochloride tablets until the constipation resolves. They may be restarted at 0.5 mg once a day. If constipation recurs at the lower dose, aloe setron hydrochloride tablets should be discontinued immediately.

Patients well controlled on 0.5 mg once or twice a day may be maintained on this regimen. If after 4 weeks the dosage is well tolerated but does not adequately control IBS symptoms, then the dosage can be increased to up to 1 mg twice a day. **Alosetron hydrochloride tablets should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice a day.**

Alosetron hydrochloride tablets can be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Alosetron hydrochloride tablets should be discontinued immediately in patients who develop constipation or signs of ischemic colitis. Alosetron hydrochloride tablets should not be restarted in patients who develop ischemic colitis.

Clinical trial and postmarketing experience suggest that debilitated patients or patients taking additional medications that decrease gastrointestinal motility may be at greater risk of serious complications of constipation. Therefore, appropriate caution and follow-up should be exercised if aloe setron hydrochloride tablets are prescribed for these patients.

Postmarketing experience suggests that elderly patients may be at greater risk for complications of constipation; therefore, appropriate caution and follow-up should be exercised if aloe setron hydrochloride tablets are prescribed for these patients *[see Warnings and Precautions (5.1)]*.

2.2 Patients With Hepatic Impairment

Alosetron hydrochloride tablets are extensively metabolized by the liver, and increased exposure to aloe setron hydrochloride tablets are likely to occur in patients with hepatic impairment. Increased drug exposure may increase the risk of serious adverse reactions. Alosetron hydrochloride tablets should be used with caution in patients with mild or moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment *[see Contraindications (4), Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

0.5 mg and 1 mg tablets

Alosetron hydrochloride tablets, 0.5 mg (0.562 mg aloe setron HCl equivalent to 0.5 mg aloe setron), are white, oval, film-coated tablets debossed “P” on one side and “819” on the other side.

Alosetron hydrochloride tablets, 1 mg (1.124 mg aloe setron HCl equivalent to 1 mg aloe setron), are blue, oval, film-coated tablets debossed with “P” on one side and “820” on the other side.

4 CONTRAINDICATIONS

4.1 Constipation

Alosetron hydrochloride should not be initiated in patients with constipation *[see Warnings and Precautions (5.1)]*.

4.2 History of Severe Bowel or Hepatic Disorders

Alosetron hydrochloride is contraindicated in patients with a history of the following:

- chronic or severe constipation or sequelae from constipation
- intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions
- ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state
- Crohn's disease or ulcerative colitis
- diverticulitis
- severe hepatic impairment

4.3 Concomitant Use of Fluvoxamine

Concomitant administration of aloe setron hydrochloride with fluvoxamine is contraindicated. Fluvoxamine, a known strong inhibitor of CYP1A2, has been shown to increase mean aloe setron plasma concentrations (AUC) approximately 6-fold and prolong the half-life by approximately 3-fold *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Complications of Constipation

Some patients have experienced serious complications of constipation without warning.

Serious complications of constipation, including obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia, have been reported with use of aloe setron hydrochloride during clinical trials. Complications of constipation have been reported with use of 1 mg twice daily and with lower doses. A dose response relationship has not been established for serious complications of constipation. **The incidence of serious complications of constipation was approximately 0.1% (1 per 1,000 patients) in women receiving either aloe setron hydrochloride tablets or placebo.** In addition, rare cases of perforation and death have been reported from postmarketing clinical practice. In some cases, complications of constipation required intestinal surgery, including colectomy. Patients who are elderly, debilitated, or taking additional medications that decrease gastrointestinal motility may be at greater risk for complications of constipation.

Alosetron hydrochloride should be discontinued immediately in patients who develop constipation *[see Boxed Warning]*.

5.2 Ischemic Colitis

Some patients have experienced ischemic colitis without warning.

Ischemic colitis has been reported in patients receiving aloe setron hydrochloride in clinical trials as well as during marketed use of the drug. **In IBS clinical trials, the cumulative incidence of ischemic colitis in women receiving aloe setron hydrochloride was 0.2% (2 per 1,000 patients, 95% confidence interval 1 to 3) through 3 months and was 0.3% (3 per 1,000 patients, 95% confidence interval 1 to 4) through 6 months.** Ischemic colitis has been reported with use of 1 mg twice daily and with lower doses. A dose-response relationship has not been established. Ischemic colitis was reported in one patient receiving placebo. The patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking aloe setron hydrochloride for longer than 6 months.

Alosetron hydrochloride should be discontinued immediately in patients with signs of ischemic colitis such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain. Because ischemic colitis can be life-threatening, patients with signs or symptoms of ischemic colitis should be evaluated promptly and have appropriate diagnostic testing performed. Treatment with aloe setron hydrochloride should not be resumed in patients who develop ischemic colitis.

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in other sections of the label:

- Complications of constipation *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Ischemic colitis *[see Boxed Warning, Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

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

8.3 Nursing Mothers

- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Dose-Ranging Study
- 14.2 Efficacy Studies
- 14.3 Long-Term Use

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

Patients With Irritable Bowel Syndrome:

Table 1 summarizes adverse reactions from 22 repeat-dose studies in patients with IBS who were treated with 1 mg of aloe setron hydrochloride twice daily for 8 to 24 weeks. The adverse reactions in **Table 1** were reported in 1% or more of patients who received aloe setron hydrochloride and occurred more frequently on aloe setron hydrochloride tablets than on placebo. A statistically significant difference was observed for constipation in patients treated with aloe setron hydrochloride tablets compared to placebo (p<0.0001).

Table 1. Adverse Reactions Reported in ≥1% of Patients With Irritable Bowel Syndrome and More Frequently on Alosetron Hydrochloride 1 mg Twice Daily Than Placebo

Body System Adverse Reaction	Placebo (n = 2,363)	Alosetron Hydrochloride 1 mg twice daily (n = 8,328)
Gastrointestinal		
Constipation	6%	29%
Abdominal discomfort and pain	4%	7%
Nausea	5%	6%
Gastrointestinal discomfort and pain	3%	5%
Abdominal distention	1%	2%
Regurgitation and reflux	2%	2%
Hemorrhoids	1%	2%

Gastrointestinal: Constipation is a frequent and dose-related side effect of treatment with aloe setron hydrochloride *[see Warnings and Precautions (5.1)]*. In clinical studies constipation was reported in approximately 29% of patients with IBS treated with aloe setron hydrochloride 1 mg twice daily (n = 9,316). This effect was statistically significant compared to placebo (p<0.0001). Eleven percent (11%) of patients treated with aloe setron hydrochloride 1 mg twice daily withdrew from the studies due to constipation. Although the number of patients with IBS treated with aloe setron hydrochloride 0.5 mg twice daily is relatively small (n = 243), only 11% of those patients reported constipation and 4% withdrew from clinical studies due to constipation. Among the patients treated with aloe setron hydrochloride 1 mg twice daily who reported constipation, 75% reported a single episode and most reports of constipation (70%) occurred during the first month of treatment, with the median time to first report of constipation onset of 8 days. Occurrences of constipation in clinical trials were generally mild to moderate in intensity, transient in nature, and resolved either spontaneously with continued treatment or with an interruption of treatment. However, serious complications of constipation have been reported in clinical studies and in postmarketing experience *[see Boxed Warning and Warnings and Precautions (5.1)]*. In Studies 1 and 2, 9% of patients treated with aloe setron hydrochloride reported constipation and 4 consecutive days with no bowel movement *[see Clinical Studies (14.2)]*. Following interruption of treatment, 78% of the affected patients resumed bowel movements within a 2-day period and were able to re-initiate treatment with aloe setron hydrochloride.

Hepatic: A similar incidence in elevation of ALT (>2-fold) was seen in patients receiving aloe setron hydrochloride or placebo (1.0% vs. 1.2%). A single case of hepatitis (elevated ALT, AST, alkaline phosphatase, and bilirubin) without jaundice in a patient receiving aloe setron hydrochloride was reported in a 12-week study. A causal association with aloe setron hydrochloride has not been established.

Long-Term Safety: Patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking aloe setron hydrochloride for longer than 6 months.

Women With Severe Diarrhea-Predominant Irritable Bowel Syndrome:

Table 2 summarizes the gastrointestinal adverse reactions from 1 repeat-dose study in female patients with severe diarrhea-predominant IBS who were treated for 12 weeks. The adverse reactions in **Table 2** were reported in 3% or more of patients who received aloe setron hydrochloride and occurred more frequently with aloe setron hydrochloride than with placebo. Other events reported in 3% or more of patients who received aloe setron hydrochloride and occurring more frequently with aloe setron hydrochloride than with placebo included upper respiratory tract infection, viral gastroenteritis, muscle spasms, headaches and fatigue.

Table 2. Gastrointestinal Adverse Reactions Reported in ≥3% of Women With Severe Diarrhea-Predominant Irritable Bowel Syndrome and More Frequently on Alosetron Hydrochloride Than Placebo.

Adverse Reaction	Placebo (n = 176)	Alosetron hydrochloride 0.5 mg once daily (n = 175)	Alosetron hydrochloride 1 mg once daily (n = 172)	Alosetron hydrochloride 1 mg twice daily (n = 176)
Constipation	5%	9%	16%	19%
Abdominal pain	3%	5%	6%	7%
Diarrhea	2%	3%	2%	2%
Hemorrhoidal				
hemorrhage	2%	3%	2%	2%
Flatulence	2%	2%	1%	3%
Hemorrhoids	2%	1%	1%	3%
Abdominal pain				
upper	1%	3%	1%	1%

Adverse reactions reported in another study of 701 women with severe diarrhea-predominant IBS were similar to those shown in **Table 2**. Gastrointestinal adverse reactions reported in 3% or more of patients who received aloe setron hydrochloride and occurring more frequently with aloe setron hydrochloride than with placebo included constipation (14% and 10% of patients taking aloe setron hydrochloride 1 mg twice daily or 0.5 mg as needed, respectively, compared with 2% taking placebo), abdominal pain, nausea, vomiting, and flatulence. Other events reported in 3% or more of patients who received aloe setron hydrochloride and occurring more frequently with aloe setron hydrochloride than with placebo included nasopharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection

- about any allergies that you have. See the end of the Medication Guide for a complete list of ingredients in aloesetron hydrochloride tablets.
- if you are pregnant, planning to get pregnant, or breastfeeding.

5. How should I take aloesetron hydrochloride tablets?

- Take aloesetron hydrochloride tablets exactly as your doctor prescribes it. You can take aloesetron hydrochloride tablets with or without food.
- Begin with 0.5 mg two times a day for 4 weeks to see how aloesetron hydrochloride tablets affects you. You and your doctor may decide that you should keep taking this dose if you are doing well.
- Check with your doctor 4 weeks after starting aloesetron hydrochloride tablets:
 - If you try 0.5 mg two times a day for 4 weeks, it may not control your symptoms. If you do not get constipation or other side effects from aloesetron hydrochloride tablets, your doctor may increase your dose up to 1 mg two times a day.
 - If 1 mg two times a day does not work after 4 weeks, aloesetron hydrochloride tablets is not likely to help you. You should stop taking it and call your doctor.
- If you miss a dose of aloesetron hydrochloride tablets**, just skip that dose. Do **not** take 2 doses the next time. Wait until the next time you are supposed to take it and then take your normal dose.
- Follow the important instructions in the section “What is the most important information I should know about aloesetron hydrochloride tablets?”** about when you must stop taking the medicine and when you should call your doctor.
- If you see other doctors** about your IBS or side effects from aloesetron hydrochloride tablets, tell the doctor who prescribed aloesetron hydrochloride tablets.

6. What are the possible side effects of aloesetron hydrochloride tablets?

Constipation is the most common side effect among women with IBS who take aloesetron hydrochloride tablets. **Some patients have developed serious bowel side effects while taking aloesetron hydrochloride tablets.** Read the section **“What is the most important information I should know about aloesetron hydrochloride tablets?”** at the beginning of this Medication Guide for information about the serious side effects you may get with aloesetron hydrochloride tablets.

This Medication Guide does not tell you about all the possible side effects of aloesetron hydrochloride tablets. Your doctor or pharmacist can give you a more complete list.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

7. How should I store aloesetron hydrochloride tablets?

- Store aloesetron hydrochloride tablets between 59° to 86°F (15° to 30°C).
- Protect aloesetron hydrochloride tablets from light and getting wet (moisture).

Keep aloesetron hydrochloride tablets and all medicines out of the reach of children.

8. General information about the safe and effective use of aloesetron hydrochloride tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any questions or concerns about aloesetron hydrochloride tablets, ask your doctor. Do not use aloesetron hydrochloride tablets for a condition for which it was not prescribed. Do not share your medicine with other people. It may harm them.

Your doctor or pharmacist can give you more information about aloesetron hydrochloride tablets that was written for healthcare professionals. You can also contact the company that makes aloesetron hydrochloride tablets (toll free) at 1-800-828-9393 or at www.parpharm.com.

9. What are the ingredients of aloesetron hydrochloride tablets?

Active Ingredient: aloesetron hydrochloride.

Inactive Ingredients: lactose anhydrous, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The white film-coat for the 0.5 mg tablet contains hypromellose, titanium dioxide, and triacetin. The blue film-coat for the 1 mg tablet contains hypromellose, titanium dioxide, triacetin, and Fd&C Blue #2/indigo carmine aluminium lake.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Non-Site Specific: Infrequent: Malaise and fatigue, cramps, pain, temperature regulation disturbances. *Rare:* Burning sensations, hot and cold sensations, cold sensations, and fungal infections.

Psychiatry: Infrequent: Anxiety. *Rare:* Depressive moods.

Reproduction: Rare: Sexual function disorders, female reproductive tract bleeding and hemorrhage, reproductive infections, and fungal reproductive infections.

Skin: Infrequent: Sweating and urticaria. *Rare:* Hair loss and alopecia; acne and folliculitis; disorders of sweat and sebum; allergic skin reaction; eczema; skin infections; dermatitis and dermatosis; and nail disorders.

Urology: Infrequent: Urinary frequency. *Rare:* Bladder inflammation, polyuria and diuresis; and urinary tract hemorrhage.

6.2 Postmarketing Experience

In addition to events reported in clinical trials, the following events have been identified during use of aloesetron hydrochloride in clinical practice. Because they were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to aloesetron hydrochloride.

Gastrointestinal: Impaction, perforation, ulceration, small bowel mesenteric ischemia.

Neurological: Headache.

Skin: Rash.

7 DRUG INTERACTIONS

In vivo data suggest that aloesetron is primarily metabolized by cytochrome P450 (CYP) 1A2, with minor contributions from CYP3A4 and CYP2C9. Therefore, inducers or inhibitors of these enzymes may change the clearance of aloesetron.

7.1 CYP1A2 Inhibitors

Fluvoxamine is a known strong inhibitor of CYP1A2 and also inhibits CYP3A4, CYP2C9, and CYP2C19. In a pharmacokinetic study, 40 healthy female subjects received fluvoxamine in escalating doses from 50 to 200 mg/day for 16 days, with coadministration of aloesetron 1 mg on the last day. Fluvoxamine increased mean aloesetron plasma concentrations (AUC) approximately 6-fold and prolonged the half-life by approximately 3-fold. Concomitant administration of aloesetron and fluvoxamine is contraindicated [see *Contraindications* (4.3)].

Concomitant administration of aloesetron and moderate CYP1A2 inhibitors, including quinolone antibiotics and cimetidine, has not been evaluated, but should be avoided unless clinically necessary because of similar potential drug interactions.

7.2 CYP3A4 Inhibitors

Ketoconazole is a known strong inhibitor of CYP3A4. In a pharmacokinetic study, 38 healthy female subjects received ketoconazole 200 mg twice daily for 7 days, with coadministration of aloesetron 1 mg on the last day. Ketoconazole increased mean aloesetron plasma concentrations (AUC) by 29%. Caution should be used when aloesetron and ketoconazole are administered concomitantly. Coadministration of aloesetron and strong CYP3A4 inhibitors such as clarithromycin, telithromycin, protease inhibitors, voriconazole, and itraconazole has not been evaluated but should be undertaken with caution because of similar potential drug interactions. The effect of induction or inhibition of other pathways on exposure to aloesetron and its metabolites is not known.

7.3 Other CYP Enzymes

In vitro human liver microsome studies and an *in vivo* metabolic probe study demonstrated that aloesetron did not inhibit CYP enzymes 3A4, 2C9, or 2C19. *In vitro* at total drug concentrations 27-fold higher than peak plasma concentrations observed with the 1 mg dose, aloesetron inhibited CYP enzymes 1A2 (60%) and 2E1 (50%). In an *in vivo* metabolic probe study, aloesetron did not inhibit CYP2E1 but did produce 30% inhibition of both CYP1A2 and N-acetyltransferase. Although not studied with aloesetron, inhibition of N-acetyltransferase may have clinically relevant consequences for drugs such as isoniazid, procainamide, and hydralazine. The effect on CYP1A2 was explored further in a clinical interaction study with theophylline and no effect on metabolism was observed. Another study showed that aloesetron had no clinically significant effect on plasma concentrations of the oral contraceptive agents ethinyl estradiol and levonorgestrel (CYP3A4 substrates). A clinical interaction study was also conducted with aloesetron and the CYP3A4 substrate cisapride. No significant effects on cisapride metabolism or QT interval were noted. The effects of aloesetron on monooamine oxidases and on intestinal first pass secondary to high intraluminal concentrations have not been examined. Based on the above data from *in vitro* and *in vivo* studies, it is unlikely that aloesetron will inhibit the hepatic metabolic clearance of drugs metabolized by the CYP enzymes 2C9, 2C19, or 2E1.

Aloesetron does not appear to induce the major cytochrome P450 drug-metabolizing enzyme 3A. Aloesetron also does not appear to induce CYP enzymes 2E1 or 2C19. It is not known whether aloesetron might induce other enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 40 mg/kg/day (about 160 times the recommended human dose based on body surface area) and rabbits at oral doses up to 30 mg/kg/day (about 240 times the recommended daily human dose based on body surface area). These studies have revealed no evidence of impaired fertility or harm to the fetus due to aloesetron.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aloesetron hydrochloride should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Aloesetron and/or metabolites of aloesetron are excreted in the breast milk of lactating rats. It is not known whether aloesetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when aloesetron hydrochloride is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Use of aloesetron hydrochloride is not recommended in the pediatric population, based upon the risk of serious complications of constipation and ischemic colitis in adults.

8.5 Geriatric Use

In some studies in healthy men or women, plasma concentrations were elevated by approximately 40% in individuals 65 years and older compared to young adults [see *Warnings and Precautions* (5.1)]. However, this effect was not consistently observed in men.

Postmarketing experience suggests that elderly patients may be at greater risk for complications of constipation therefore, appropriate caution and follow-up should be exercised if aloesetron hydrochloride is prescribed for these patients [see *Warnings and Precautions* (5.1)].

8.6 Hepatic Impairment

Due to the extensive hepatic metabolism of aloesetron, increased exposure to aloesetron and/or its metabolites is likely to occur in patients with hepatic impairment. Aloesetron should not be used in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate hepatic impairment.

A single 1 mg oral dose of aloesetron was administered to 1 female and 5 male patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) and to 1 female and 2 male patients with severe hepatic impairment (Child-Pugh score of ≥9). In comparison with historical data from healthy subjects, patients with severe hepatic impairment displayed higher systemic exposure to aloesetron. The female with severe hepatic impairment displayed approximately 14-fold higher exposure, while the female with moderate hepatic impairment displayed approximately 1.6-fold higher exposure, than healthy females. Due to the small number of subjects and high intersubject variability in the pharmacokinetic findings, no definitive quantitative conclusions can be made. However, due to the greater exposure to aloesetron in the female with severe hepatic impairment, aloesetron should not be used in females with severe hepatic impairment [see *Dosage and Administration* (2.2), *Contraindications* (4)].

8.7 Renal Impairment

Renal impairment (creatinine clearance 4 to 56 mL/min) has no effect on the renal elimination of aloesetron due to the minor contribution of this pathway to elimination. The effect of renal impairment on metabolite pharmacokinetics and the effect of end-stage renal disease have not been assessed.

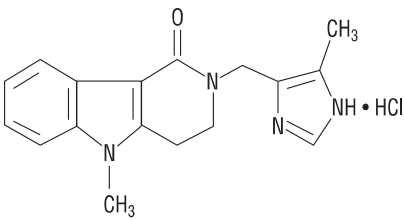
10 OVERDOSAGE

There is no specific antidote for overdose of aloesetron hydrochloride. Patients should be managed with appropriate supportive therapy. Individual oral doses as large as 16 mg have been administered in clinical studies without significant adverse reactions. This dose is 8 times higher than the recommended total daily dose. Inhibition of the metabolic elimination and reduced first pass of other drugs might occur with overdoses of aloesetron hydrochloride [see *Drug Interactions* (7)].

11 DESCRIPTION

The active ingredient in aloesetron hydrochloride tablets is aloesetron hydrochloride (HCl), a potent and selective antagonist of the serotonin 5-HT₁ receptor type. Chemically, aloesetron is designated as 2,3,4,5-tetrahydro-5-methyl-2-[5-(methyl-1H-imidazol-4-yl)methyl]-1H-pyrrolo[4,3-b]pyridol-1-one, monohydrochloride. Aloesetron is achiral and has the empirical formula C₁₁H₁₁N₄O•HCl, representing a molecular weight of 330.8.

Aloesetron is a white to beige powder that has a solubility of 61 mg/mL in water, 42 mg/mL in 0.1M hydrochloric acid, 0.3 mg/mL in pH 6 phosphate buffer, and <0.1 mg/mL in pH 8 phosphate buffer. The chemical structure of aloesetron is:



Aloesetron hydrochloride tablets are supplied for oral administration as 0.5 mg (white) and 1 mg (blue) tablets. The 0.5 mg tablet contains 0.562 mg aloesetron HCl equivalent to 0.5 mg aloesetron, and the 1 mg tablet contains 1.124 mg aloesetron HCl equivalent to 1 mg of aloesetron. Each tablet also contains the inactive ingredients lactose anhydrous, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The white film-coat for the 0.5 mg tablet contains hypromellose, titanium dioxide, and triacetin. The blue film-coat for the 1 mg tablet contains hypromellose, titanium dioxide, triacetin, and Fd&C Blue #2/indigo carmine aluminium lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Aloesetron is a potent and selective 5-HT₁ receptor antagonist. 5-HT₁ receptors are ligand-gated cation channels that are extensively distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and central locations. Activation of these channels and the resulting neuronal depolarization affect the regulation of visceral pain, colonic transit, and gastrointestinal secretions, processes that relate to the pathophysiology of IBS. 5-HT₁ receptor antagonists such as aloesetron inhibit activation of non-selective cation channels, which results in the modulation of the enteric nervous system.

The cause of IBS is unknown. IBS is characterized by visceral hypersensitivity and hyperactivity of the gastrointestinal tract, which lead to abnormal sensations of pain and motor activity. Following distention of the rectum, patients with IBS exhibit pain and discomfort at lower volumes than healthy volunteers. Following such distention, aloesetron reduced pain and exaggerated motor responses, possibly due to blockade of 5-HT₁ receptors.

12.2 Pharmacodynamics

In healthy volunteers and patients with IBS, aloesetron (2 mg orally, twice daily for 8 days) increased colonic transit time without affecting orocecal transit time. In healthy volunteers, aloesetron also increased basal jejunal water and sodium absorption after a single 4 mg dose. In patients with IBS, multiple oral dosages of aloesetron (4 mg twice daily for 6.5 days) significantly increased colonic compliance.

Single oral doses of aloesetron administered to healthy men produced a dose-dependent reduction in the flare response seen after intradermal injection of serotonin. Urinary 6- β -hydroxycortisol excretion decreased by 52% in elderly subjects after 27.5 days of aloesetron 2 mg administered orally twice daily. This decrease was not statistically significant. In another study utilizing aloesetron 1 mg administered orally twice daily for 4 days, there was a significant decrease in urinary 6- β -hydroxycortisol excretion. However, there was no change in the ratio of 6- β -hydroxycortisol to cortisol, indicating a possible decrease in cortisol production. The clinical significance of these findings is unknown.

12.3 Pharmacokinetics

The pharmacokinetics of aloesetron have been studied after single oral doses ranging from 0.05 to 16 mg in healthy men. The pharmacokinetics of aloesetron have also been evaluated in healthy women and men and in patients with IBS after repeated oral dosages ranging from 1 mg twice daily to 8 mg twice daily.

Absorption: Aloesetron was rapidly absorbed after oral administration with a mean absolute bioavailability of approximately 50% to 60% (approximate range, 30% to >90%). After administration of radiolabeled aloesetron, only 1% of the dose was recovered in the feces as unchanged drug. Following oral administration of a 1 mg aloesetron dose to young men, a peak plasma concentration of approximately 5 ng/mL occurred at 1 hour. In young women, the mean peak plasma concentration was approximately 9 ng/mL, with a similar time to peak.

Plasma concentrations were 30% to 50% lower and less variable in men compared to women given the same oral dose. Population pharmacokinetic analysis in IBS patients confirmed that aloesetron concentrations were influenced by gender (27% lower in men).

Food Effects: Aloesetron absorption is decreased by approximately 25% by coadministration with food, with a mean delay in time to peak concentration of 15 minutes [see *Dosage and Administration* (2.1)].

Distribution: Aloesetron demonstrates a volume of distribution of approximately 65 to 95 L. Plasma protein binding is 82% over a concentration range of 20 to 4,000 ng/mL.

Metabolism and Elimination: Plasma concentrations of aloesetron increase proportionately with increasing single oral doses up to 8 mg and more than proportionately at a single oral dose of 16 mg. Twice-daily oral dosing of aloesetron does not result in accumulation. The terminal elimination half-life of aloesetron is approximately 1.5 hours (plasma clearance is approximately 600 mL/min). Population pharmacokinetic analysis in patients with IBS confirmed that aloesetron clearance is minimally influenced by doses up to 8 mg.

Renal elimination of unchanged aloesetron accounts for only 13% of the dose. Renal clearance is approximately 112 mL/min.

A study with ¹⁴C-labeled aloesetron in Caucasian males (n = 3) and females (n = 3) and an Asian male (n = 1) showed similar serum metabolite profiles. Unchanged aloesetron was the major component in serum, with other metabolites being present at low concentrations, none amounting to more than 15% of the unmetabolized aloesetron concentration. The circulating metabolites were identified as 6-hydroxy glucuronide, 6-hydroxy sulphate, 7-hydroxy sulphate, hydroxymethyl imidazole, and mono- and bis-oxygenated imidazole derivatives of aloesetron. The metabolites are unlikely to contribute to the biological activity of aloesetron. Of the circulating Phase I metabolites, only the hydroxymethyl imidazole has weak pharmacological activity, around 10-fold less potent than aloesetron. Total recovery of radioactivity in the excreta was 85 ± 6%. The majority of the radiolabeled dose is excreted in the urine (74 ± 5%). The major urinary metabolites were the 6-hydroxy glucuronide and the mono- and bis-oxygenated imidazole derivatives of aloesetron. 11 ± 4% of the radiolabeled dose was excreted in the feces with less than 1% of the dose being excreted as the unchanged aloesetron.

Aloesetron is metabolized by human microsomal cytochrome P450 (CYP), shown *in vitro* to involve enzymes 2C9 (30%), 3A4 (18%), and 1A2 (10%). Non-CYP-mediated Phase I metabolic conversion also contributes to an extent of about 11%. However, *in vivo* data suggest that CYP1A2 plays a more prominent role in aloesetron metabolism (62 to 97% of aloesetron clearance) based on correlation of aloesetron clearance with *in vivo* CYP1A2 activity measured by probe substrate, increased clearance induced by smoking, and inhibition of clearance by fluvoxamine [see *Contraindications* (4), *Drug Interactions* (7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year oral studies, aloesetron was not carcinogenic in mice at doses up to 30 mg/kg/day or in rats at doses up to 40 mg/kg/day. These doses are about 60 to 160 times, respectively, the recommended human dose of aloesetron of 2 mg/day (1 mg twice daily) based on body surface area. Aloesetron was not genotoxic in the Ames tests, the mouse lymphoma cell (L5178Y/TK) forward gene mutation test, the human lymphocyte chromosome aberration test, the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, or the *in vivo* rat micronucleus test for mutagenicity. Aloesetron at oral doses up to 40 mg/kg/day (about 160 times the recommended daily human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male or female rats.

14 CLINICAL STUDIES

14.1 Dose-Ranging Study

Data from a dose-ranging study of women (n = 85) who received aloesetron hydrochloride 0.5 mg twice daily indicated that the incidence of constipation (14%) was lower than that experienced by women receiving 1 mg twice daily (29%). Therefore, to lower the risk of constipation, aloesetron hydrochloride should be started at a dosage of 0.5 mg twice a day. The efficacy of the 0.5 mg twice-daily dosage in treating severe diarrhea-predominant IBS has not been adequately evaluated in clinical trials. [see *Dosage and Administration* (2.1)]

14.2 Efficacy Studies

Aloesetron hydrochloride has been studied in women with IBS in five 12-week US multicenter, randomized, double-blind, placebo-controlled clinical studies.

Study	Patient Population	Placebo (n)	Aloe setron Hydrochloride Dose (n)
1 and 2	Non-constipated women with IBS	(640)	1 mg twice daily (633)
3 and 4	Women with severe diarrhea-predominant IBS (defined as bowel urgency \geq 50% of days)	(515)	1 mg twice daily (778)
5	Women with severe diarrhea-predominant IBS (defined as average pain \geq moderate, urgency \geq 50% of days, and/or restriction of daily activities \geq 25% of days)	(176)	0.5 mg once daily (177)
			1 mg once daily (175)
			1 mg twice daily (177)

Studies in Non-Constipated Women with Irritable Bowel Syndrome: Studies 1 and 2 were conducted in non-constipated women with IBS meeting the Rome Criteria[®] for at least 6 months. Women with severe pain or a history of severe constipation were excluded. A 2-week run-in period established baseline IBS symptoms.

About two thirds of the women had diarrhea-predominant IBS. Compared with placebo, 10% to 19% more women with diarrhea-predominant IBS who received aloesetron hydrochloride had adequate relief of IBS abdominal pain and discomfort during each month of the study.

Studies in Women With Severe Diarrhea-Predominant Irritable Bowel Syndrome: Aloesetron hydrochloride is indicated only for women with severe diarrhea-predominant IBS [see *Indications And Usage* (1)]. The efficacy of aloesetron hydrochloride in this subset of the women studied in clinical trials is supported by prospective and retrospective analyses.

Prospective Analyses: Studies 3 and 4 were conducted in women with diarrhea-predominant IBS and bowel urgency on at least 50% of days at entry. Women receiving aloesetron hydrochloride had significant increases over placebo (13% to 16%) in the median percentage of days with urgency control.

The lower gastrointestinal functions of stool consistency, stool frequency, and sense of incomplete evacuation were also evaluated by patients' daily reports. Stool consistency was evaluated on a scale of 1 to 5 (1 = very hard, 2 = hard, 3 = formed, 4 = loose, and 5 = watery). At baseline, average stool consistency was approximately 4 (loose) for both treatment groups. During the 12 weeks of treatment, the average stool consistency decreased to approximately 3.0 (formed) for patients who received aloesetron hydrochloride and 3.5 for the patients who received placebo in the 2 studies.

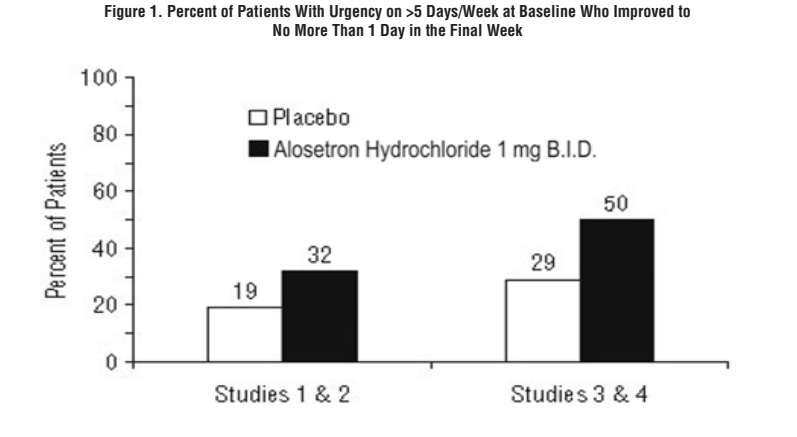
At baseline, average stool frequency was approximately 3.2 per day for both treatment groups. During the 12 weeks of treatment, the average daily stool frequency decreased to approximately 2.1 and 2.2 for patients receiving aloesetron hydrochloride and 2.7 and 2.8 for patients receiving placebo in the 2 studies.

There was no consistent effect upon the sense of incomplete evacuation during the 12 weeks of treatment for patients receiving aloesetron hydrochloride as compared to patients receiving placebo in either study.

Study 5 was conducted in women with severe diarrhea-predominant IBS and 1 or more of the following: frequent and severe abdominal pain or discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS. To evaluate the proportion of patients who responded to treatment, patients were asked every 4 weeks to compare their IBS symptoms during the previous month of treatment with how they usually felt during the 3 months prior to the study using an ordered 7-point scale (substantially worse to substantially improved). A responder was defined as a subject who reported moderate or substantial improvement on this global improvement scale (GIS). At Week 12, all three groups receiving aloesetron hydrochloride had significantly greater percentages of GIS responders compared to the placebo group (43% to 51% vs. 31%) using a Last Observation Carried Forward (LOCF) analysis. It should be noted that approximately 4% of subjects in each aloesetron hydrochloride dose group who were classified as responders using this approach were observed only through week 4. At each of the 4 week intervals of the treatment phase, all three dosages of aloesetron hydrochloride provided improvement in the average adequate relief rate of IBS pain and discomfort, stool consistency, stool frequency, and sense of urgency compared with placebo.

Retrospective Analyses: In analyses of patients from Studies 1 and 2 who had diarrhea-predominant IBS and indicated their baseline run-in IBS symptoms were severe at the start of the trial, aloesetron hydrochloride provided greater adequate relief of IBS pain and discomfort than placebo. In further analyses of Studies 1 and 2, 57% of patients had urgency at baseline on 5 or more days per week. In this subset, 32% of patients on aloesetron hydrochloride had urgency no more than 1 day in the last week of the trial, compared with 19% of patients on placebo.

In Studies 3 and 4, 66% of patients had urgency at baseline on 5 or more days per week. In this subset, 50% of patients on aloesetron hydrochloride had urgency no more than 1 day in the last week of the trial, compared with 29% of patients on placebo. Moreover, in the same subset, 12% on aloesetron hydrochloride had urgency no more than 2 days per week in any of the 12 weeks on treatment compared with 1% of placebo patients.



In Studies 1 and 2, patient-reported subjective outcomes related to IBS were assessed by questionnaires obtained at baseline and week 12. Patients in the more severe subset who received aloesetron hydrochloride reported less difficulty sleeping, less tiredness, fewer eating problems, and less interference with social activities and work/main activities due to IBS symptoms or problems compared to