DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Mark vB. Cleveland, PhD.
Vice President
New Product Development
Braintree Laboratories, Inc.
60 Columbian Street West
P.O. Box 850929
Braintree, MA 02185-0929

RE: **MIRALAX (polyethylene glycol 3350 NF Powder)**
NDA 20-698
MACMIS ID # 9769

Dear Dr. Cleveland:

This letter concerns Braintree Laboratories, Inc.'s (Braintree) dissemination of promotional materials for MiraLax (polyethylene glycol 3350 NF Powder.) The Division of Drug Marketing, Advertising and Communications (DDMAC), as part of its monitoring program, has reviewed MiraLax promotional materials consisting of a Journal Advertisement (Ad) [TRE-0581R2], a Sell Sheet [TRE-0571], a Dear Director of Nursing Letter, a Brochure [D499], a Notepad, a Puzzle, and a MiraLax website (identified as http://www.miralax.com), and has concluded that Braintree is disseminating materials that contain misleading promotional claims in violation of the Federal Food, Drug, and Cosmetic Act and implementing regulations. A description of our objections follows. These objections are meant to apply to all other MiraLax materials containing the same or similar claims.

Unsubstantiated Mechanisms of Action

The claim that MiraLax "works in 4 ways" is a misleading representation of MiraLax's mechanism of action in the treatment of constipation. MiraLax is an osmotic agent that softens the stool and increases the frequency of bowel movements by retaining water in the stool. MiraLax has not been proven to provide bulk or lubrication in the relief of constipation. The Journal Ad states that "*MiraLax [has] Softening, Lubricating, Bulking, and Osmotic*

Actions All in One," and that it "*acts like a 4-in-1 laxative.*" This claim is misleading because it is not supported by substantial evidence.

Misleading Onset of Action Claims

The claim that MiraLax "*results in regular bowel movements within 2-4 days,*" as stated in the Dear Director of Nursing Letter, is misleading because it does not communicate that MiraLax may not produce an initial bowel movement until 2-4 days after ingestion. Also, in one of the clinical studies used as the basis for approval, MiraLax did not demonstrate superiority over placebo in relieving constipation until the second week of therapy.

Unsubstantiated Superiority Claims

The claim that MiraLax is superior to stimulant laxatives is misleading because it is not supported by head-to-head controlled trials and is inconsistent with the approved product labeling for MiraLax. For example, the Dear Director of Nursing Letter states: "*Nursing staff may hear fewer complaints with MiraLax. As opposed to harsh stimulants which typically increase the likelihood of soiling linens, MiraLax is gentle and predictable resulting in regular bowel movements within 2-4 days.*" The Precautions section of the approved product labeling for MiraLax, however, states that "*In geriatric nursing home patients a higher incidence of diarrhea occurred at the recommended 17 gram dose. If diarrhea occurs, MiraLax should be discontinued.*"

The claim that MiraLax is superior to nonprescription fiber laxatives is also misleading because it is unsubstantiated. The MiraLax Brochure entitled "*Tired of Complaints Concerning Fiber Therapy?*" states that "*MiraLax has the clear advantage over fiber.*" The comparative chart that follows this claim makes selective comparisons between MiraLax and fiber laxatives, and suggests that MiraLax is superior to fiber laxatives because MiraLax has "no grit," for example. These comparisons are misleading because they suggest that prescription MiraLax and nonprescription fiber laxatives share similar efficacy and/or safety profiles and because there is no substantial evidence demonstrating the superiority of MiraLax.

Misleading Comparisons

Preference Claims - A patient preference claim that appears in the MiraLax Sell Sheet depicts blurred but discernable images of containers of Metamucil and Citrucel next to a sharply focused picture of MiraLax. The headline reads, "*Which Laxative Would Your Patients Prefer?*" followed by a chart that selectively presents and compares presumed preference features of MiraLax vs. Fiber (e.g. Metamucil and Citrucel). This comparative preference claim is misleading because it suggests that patients prefer MiraLax to Metamucil and Citrucel without data to provide adequate substantiation for this claim.

Cost Savings Claims – A chart appears in the Dear Director of Nursing Letter that compares the (daily, weekly, and annual) costs of therapy with MiraLax to the therapy costs associated with all other OTC laxatives. The chart is misleading because it implies that all costs associated with laxative therapy have been evaluated, not simply the acquisition price of the

drug. The chart also implies that efficacy and/or outcomes of the different therapies are the same without supporting evidence. The chart also does not disclose that retail or wholesale prices listed do not necessarily correlate with the price actually paid for the drugs by a pharmacy or consumer.

Lack of Fair Balance

These MiraLax promotional materials are misleading because they fail to present information relating to contraindications, warnings, precautions, and side effects associated with the use of MiraLax with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug. Several examples of lack of fair balance follow:

- The Journal Ad prominently presents efficacy claims for MiraLax, such as "[MiraLax] *effectively treats occasional constipation,*" and [use MiraLax] "for the treatment of occasional constipation," in bolded, easy-to-read type. The warnings, contraindications, precautions and adverse reactions, however, appear in a micro-type paragraph at the bottom of the page.

- The MiraLax Website contains a "Fact Sheet" web-page for patients, that provides extensive efficacy information about MiraLax but fails to provide any risk information. The website also contains a "Patient Information" web-page that omits precautionary information regarding the risk of electrolyte imbalance and dependence on laxatives that may result from prolonged, frequent or excessive use of MiraLax.

- The MiraLax Note Pad includes a poem that "*Once-a-day MiraLax sure does the trick...*" without providing any balancing information regarding side effects or other risk information for MiraLax. Similarly, a rubber puzzle advertises that MiraLax is a "*4 in 1 Laxative*," but provides no risk information to balance the misleading efficacy claim made.

- The Dear Director of Nursing Letter states that "*Unpleasant effects are unlikely although nausea, bloating, cramps, flatulence or diarrhea could occur.*" The approved product labeling for MiraLax, however, lists these adverse events as being the most common with MiraLax and also advises that "*In geriatric nursing home patients a higher risk of diarrhea occurred at the recommended 17 gram dose. If diarrhea occurs, MiraLax should be discontinued.*" The claim that unpleasant effects are unlikely is misleading because it minimizes the risks that are associated with MiraLax use, particularly in elderly patients.

- The Journal Ad also minimizes risks associated with MiraLax therapy. The Journal Ad presents prominent claims that MiraLax treats occasional constipation typically "*without contributing to gas or cramping*," and that "*constipated patients treated with MiraLax had a lower incidence of severe cramping (12% vs. 23%) and severe gas (24% vs. 40%) when compared to placebo.*" The approved product labeling, however, states that cramping and flatulence are two of the most common adverse events for MiraLax. The bird-size disclosure of these common adverse events that appears in running text at the bottom of the Journal Ad is insufficient to remedy the overwhelmingly misleading message that MiraLax is as safe as a placebo and does not contribute to gas or cramping.

Lack of Prominence of Established Name

Throughout the materials, the proprietary name "MiraLax" appears in large stylized font, directly above its established name, "polyethylene glycol 3350 NF powder." The font-size used for the established name is not commensurate with the prominence of the proprietary name. An established name must be printed in letters that are at least half as large as the letters comprising the proprietary name and the prominence of the established name must be commensurate with the prominence of the proprietary name.

Requested Action

In order to address these objections, DDMAC requests that Braintree do the following:

1. Immediately cease further use of these and other materials with the same or similar messages.

2. Provide DDMAC, in writing, with Braintree's intent to comply with the above. This response should include a list of all violative promotional materials and Braintree's methods for discontinuing their use.

Your written response should be received no later than April 12, 2001. If you have any questions or comments, please contact the undersigned by facsimile at (301) 594-6759, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17-B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID # 9769.

Sincerely,

Patricia Kuker Staub, R.Ph., JD
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

/s/

Patricia Staub
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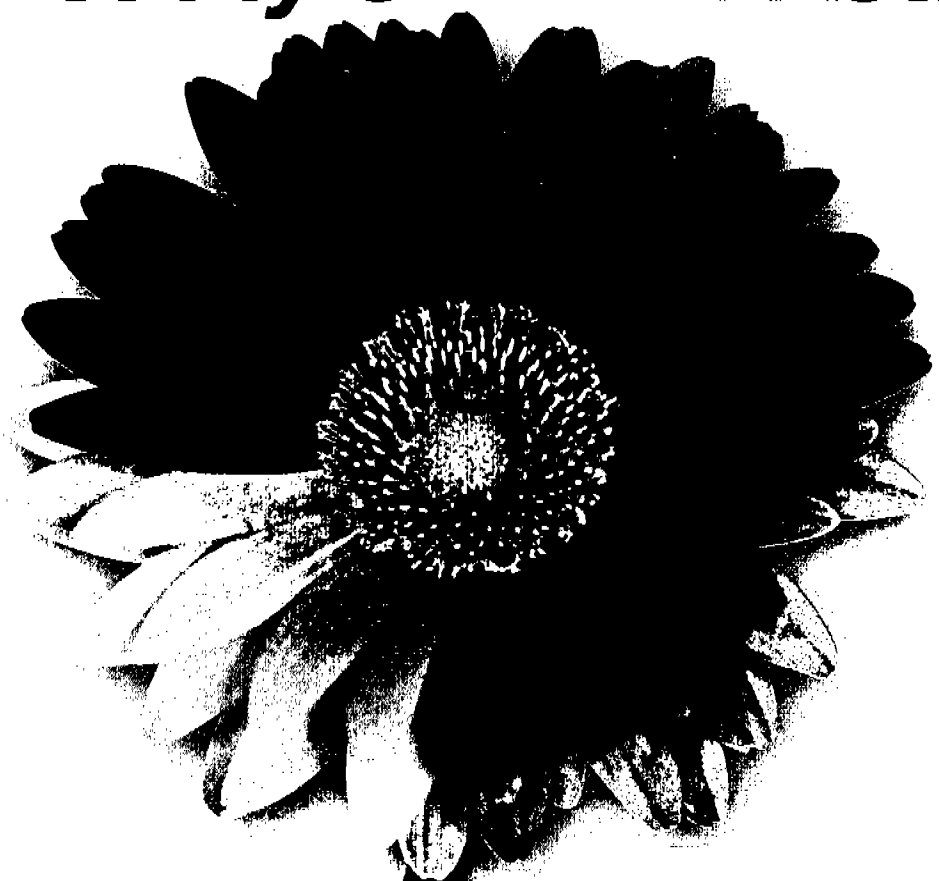
When Laxative Therapy Is Indicated...

The Beauty of 4-in-1 Action



Dissolves completely in water and has no grit, no taste, no sugar, no sweetener, and no residue

Effectively treats occasional constipation typically without contributing to gas or cramping

In a published clinical study,[1] constipated patients treated with MiraLax had a lower incidence of severe cramping (12% vs 23%), and severe gas (24% vs 40%) when compared to placebo

Softening Bulking
Lubricating Osmotic
.....Actions All In One

MiraLax™
Polyethylene Glycol 3350, NF Powder

PRESCRIPTION Rx LAXATIVE

Acts like a 4-in-1 laxative

Indications and Usage: For the treatment of occasional constipation

Most Common Adverse Events: Nausea, abdominal bloating, cramping, and flatulence (Patients should be evaluated for bowel obstruction or metabolic disorders)

Brief Summary: Before prescribing, see complete prescribing information. **INDICATIONS AND USAGE:** For the treatment of occasional constipation. This product should be used for 2 weeks or less or as directed by a physician. **CONTRAINDICATIONS:** MiraLax is contraindicated in patients with known or suspected bowel obstruction and patients known to be allergic to polyethylene glycol. **WARNINGS:** Patients with symptoms suggestive of bowel obstruction (nausea, vomiting, abdominal pain or distention) should be evaluated to rule out this condition before initiating MiraLax therapy. **PRECAUTIONS: General:** Patients presenting with complaints of constipation should have a thorough medical history and physical examination to detect associated metabolic, endocrine and neurogenic conditions, and medications. A diagnostic evaluation should include a structural evaluation of the colon. Patients should be educated about good defecatory and eating habits (such as high fiber diets) and lifestyle changes (adequate dietary fiber and fluid intake, regular exercise) which may produce more regular bowel habits. MiraLax should be administered dissolved in approximately 8 ounces of water. Safety and effectiveness in pediatric patients has not been established. MiraLax should only be administered to a pregnant woman if clearly needed. **ADVERSE REACTIONS:** Nausea, abdominal bloating, cramping and flatulence may occur. High doses may produce diarrhea and excessive stool frequency, particularly in elderly nursing home patients. Patients taking other medications containing polyethylene glycol have occasionally developed urticaria suggestive of an allergic reaction. **Rx only. STORAGE:** Store at 25°C (77°F). Distributed by Braintree Laboratories, Inc., Braintree, MA 02185.

Reference: 1. DiPalma et al. A randomized, placebo-controlled, multicenter study of the safety and efficacy of Braintree polyethylene glycol laxative. *Am J Gastroenterol.* 2000;95:446-450.

U.S. Patents No. 5,710,183; No. 6,048,901.

Medicaid Approved*
*In most states

For product samples and literature, call 1-888-MIRALAX (1-888-647-2529) or visit our Web site at www.MiraLax.com

 TRE-0581R2 October, 2000

LABORATORIES, INC Braintree

MIRALAX™
Polyethylene Glycol 3350, NF Powder

Full Prescribing Information

DESCRIPTION: A white powder for reconstitution. MiraLax (polyethylene glycol 3350, NF) is a synthetic polyglycol having an average molecular weight of 3350. The actual molecular weight is not less than 90.0 percent and not greater than 110.0 percent of the nominal value. The chemical formula is $HO(C_2H_4O)_nH$ in which n represents the average number of oxyethylene groups. Below 55°C it is a free flowing white powder freely soluble in water.
MiraLax is an osmotic agent for the treatment of constipation.

CLINICAL PHARMACOLOGY: Pharmacology: MiraLax is an osmotic agent which causes water to be retained with the stool.
Essentially, complete recovery of MiraLax was shown in normal subjects without constipation. Attempts at recovery of MiraLax in constipated patients resulted in incomplete and highly variable recovery. In vitro study showed indirectly that MiraLax was not fermented into hydrogen or methane by the colonic microflora in human feces. MiraLax appears to have no effect on the active absorption or secretion of glucose or electrolytes. There is no evidence of tachyphylaxis.

CLINICAL TRIALS: In one study, patients with less than 3 bowel movements per week were randomized to MiraLax, 17 grams, or placebo for 14 days. An increase in bowel movement frequency was observed for both treatment groups during the first week of treatment. MiraLax was statistically superior to placebo during the second week of treatment.
In another study, patients with 3 bowel movements or less per week and/or less than 300 grams of stool per week were randomized to 2 dose levels of MiraLax or placebo for 10 days each. Success was defined by an increase in both bowel movement frequency and daily stool weight. For both parameters, superiority of the 17 gram dose of MiraLax over placebo was demonstrated.

INDICATIONS AND USAGE: For the treatment of occasional constipation. This product should be used for 2 weeks or less or as directed by a physician.

CONTRAINDICATIONS: MiraLax is contraindicated in patients with known or suspected bowel obstruction and patients known to be allergic to polyethylene glycol.

WARNINGS: Patients with symptoms suggestive of bowel obstruction (nausea, vomiting, abdominal pain or distention) should be evaluated to rule out this condition before initiating MiraLax therapy.

PRECAUTIONS:
General: Patients presenting with complaints of constipation should have a thorough medical history and physical examination to detect associated metabolic, endocrine and neurogenic conditions, and medications. A diagnostic evaluation should include a structural examination of the colon. Patients should be educated about good defecatory and eating habits (such as high fiber diets) and lifestyle changes (adequate dietary fiber and fluid intake, regular exercise) which may produce more regular bowel habits.
MiraLax should be administered dissolved in approximately 8 ounces of water.

Information for Patients: MiraLax softens the stool and increases the frequency of bowel movements by retaining water in the stool. It should always be taken by mouth after being dissolved in 8 ounces of water. Should unusual cramps, bloating, or diarrhea occur, consult your physician.
Two to 4 days may be required to produce a bowel movement. This product should be used for 2 weeks or less or as directed by a physician. Prolonged, frequent or excessive use of MiraLax may result in electrolyte imbalance and dependence on laxatives.

Laboratory Tests: No clinically significant effects on laboratory tests have been demonstrated.

Drug Interactions: No specific drug interactions have been demonstrated.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term carcinogenicity studies, genetic toxicity studies and reproductive toxicity studies in animals have not been performed with MiraLax.

Pregnancy: Category C. Animal reproductive studies have not been performed with MiraLax. It is also not known whether MiraLax can cause fetal harm when administered to a pregnant woman, or can effect reproductive capacity. MiraLax should only be administered to a pregnant woman if clearly needed.

Pediatric Use: Safety and effectiveness in pediatric patients has not been established.

Geriatric Use: There is no evidence for special considerations when MiraLax is administered to elderly patients. In geriatric nursing home patients a higher incidence of diarrhea occurred at the recommended 17 g dose. If diarrhea occurs MiraLax should be discontinued.

ADVERSE REACTIONS: Nausea, abdominal bloating, cramping and flatulence may occur. High doses may produce diarrhea and excessive stool frequency, particularly in elderly nursing home patients.
Patients taking other medications containing polyethylene glycol have occasionally developed urticaria suggestive of an allergic reaction.

OVERDOSAGE: There have been no reports of accidental overdosage. In the event of overdosage diarrhea would be the expected major event. If an overdose of drug occurred without concomitant ingestion of fluid, dehydration due to diarrhea may result. Medication should be terminated and free water administered. The oral LD_{50} is >50 gm/Kg in mice, rats and rabbits.

DOSAGE AND ADMINISTRATION: The usual dose is 17 grams (about 1 heaping tablespoon) of powder per day (or as directed by physician) in 8 ounces of water. Each bottle of MiraLax is supplied with a measuring cap marked to contain 17 grams of laxative powder when filled to the indicated line.
Two to 4 days (48 to 96 hours) may be required to produce a bowel movement.

HOW SUPPLIED: In powdered form, for oral administration after dissolution in water. MiraLax is available in two package sizes; a 14 oz. container of 255 grams of laxative powder and a 26 oz. container of 527 grams of laxative powder.
The cap on each bottle is marked with a measuring line and may be used to measure a single MiraLax dose of 17 grams (about 1 heaping tablespoon).

RX ONLY
STORAGE: Store at 25 degrees C (77 degrees F); excursions permitted to 15-30 degrees C (59-86 degrees F). See USP "Controlled Room Temperature."

Distributed by Braintree Laboratories, Inc., Braintree, MA 02185

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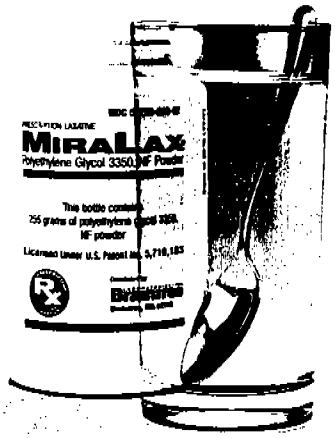
Tired of Complaints Concerning Fiber Therapy?

Challenge your senses with a

MIRALAX™

Demonstration



SUGGESTED 16823

You'll Discover...

MIRALAX™

has the
clear advantage
over fiber

	MIRALAX	fiber
NO GRIT	X	☐
NO TASTE	X	☐
DISSOLVES COMPLETELY IN WATER	X	☐
NO SUGAR/ NO SWEETENER	X	☐
NO RESIDUE	X	☐

Mix it up and see for yourself!

MIRALAX™ *vs.* fiber

MEDICAID APPROVED *in most states*

Indications and Usage
For the treatment of occasional constipation. Treatment for 2-4 days may be required to produce a bowel movement.

Most Common Adverse Events
Nausea, abdominal bloating, cramping, and flatulence. (Patients should be evaluated for bowel obstruction or metabolic disorders.)

For product samples and literature, call 1-888-MIRALAX (1-888-647-2529)
www.MiraLax.com

Consider the features of MiraLax...

MiraLax	Fiber*
No grit	—
No taste	—
Dissolves completely in water	—
No sugar/No sweetener	—
No residue	—

Most Common Adverse Events

Nausea, abdominal bloating, cramping, and flatulence (Patients should be evaluated for bowel obstruction or metabolic disorders)

Please see full prescribing information on next page.

Medicaid Approved†
†In most states

For product samples and literature, call 1-888-MIRALAX (1-888-647-2529) or visit our Web site at www.MiraLax.com

*Original texture, regular flavor Metamucil (psyllium husk fiber) is a registered trademark of Procter & Gamble. Orange Flavor Citrucel (methylcellulose) is a registered trademark of SmithKline Beecham Consumer Healthcare, L.P.

Braintree LABORATORIES, INC

November 8, 2000

Dear Director of Nursing,

Unable to solve your patient's constipation problems?

If so, we would like to introduce you to a new prescription laxative therapy, **MiraLax**™ (Polyethylene Glycol 3350, NF Powder) which combines all the benefits of softening, bulking, lubricating and osmotic actions into one laxative.

❑ Savings for VNA patients

	MiraLax	OTC[1]
▪ Cost per day:	$0.80	$1.00
▪ Cost per week:	$5.60	$7.00
▪ Cost per year (26 weeks of usage)	$145.60	$182.00
▪ Percentage covered by Medicaid/Private Insurance:	100%	0%
▪ BOTTOM LINE:	<u>$0.00</u>	<u>$182.00</u>

❑ Convenient

MiraLax is taken only once a day and is tasteless and odorless. Fiber products may need to be taken 2-3 times per day and have a gritty texture. MiraLax is highly effective, increasing the volume and frequency of bowel movements. It is gentle acting and well-tolerated.

❑ Complaints

Nursing staff may hear fewer complaints with MiraLax. As opposed to harsh stimulants which typically increase the likelihood of soiling linens, MiraLax is gentle and predictable resulting in regular bowel movements within 2-4 days.

MiraLax is indicated for the treatment of occasional constipation, and should be used for 2 weeks or less or as directed by a physician. Patients with symptoms suggestive of bowel obstruction or underlying metabolic conditions should be thoroughly evaluated before initiating MiraLax therapy. Unpleasant side effects are unlikely, although nausea, bloating, cramps, flatulence, or diarrhea could occur. Please see full prescribing information on the back of the advertisement included in this packet.

Please review MiraLax with your Medical Director and patient's Primary Physician. If you would like to know more about MiraLax, please complete the attached form and fax to 781-843-7932 or call 1-888-MiraLax. For samples of MiraLax please have a physician sign and complete the enclosed sample request card. Thank you for your support.

Sincerely,

Lynne Gagne
Product Manager

[1] Red Book, October 2000

60 Columbian Street West, P.O. Box 850929, Braintree, MA 02185-0929 • www.braintreelabs.com •

545GEN ID 18750

1ST NEW Rx LAXATIVE THERAPY IN 23 YEARS

MiraLax™ Polyethylene Glycol 3350, NF Powder Rx

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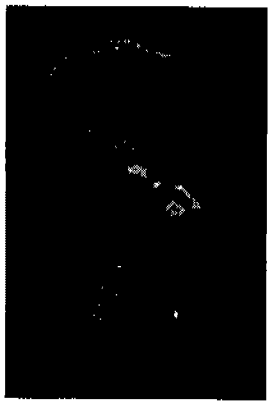
MiraLax
Laxatives
Constipation
FAQs
Patient Instructions
Contact Us
Links
Site Map

FACT SHEET

- **No grit**
- **No taste**
- **Colorless**
- **Easy to take**
- **Mix 17 g powder in 8 oz. water**

Note: MiraLax is a prescription drug, see your doctor for complete information.



Constipation affects nearly 20% of the general population and every year, more than 4 million people in the United States seek care.

With it's simple once-a-day dosing and it's unique tasteless and odorless formula, MiraLax is gentle acting and well - tolerated.

Many people who suffer from constipation do so in silence and without treatment. MiraLax provides options to those in need.

Home
MiraLax
Laxatives
Constipation
FAQs
Patient Instructions
Contact Us
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What Causes Constipation?

An alteration or deviation form a normal routine may result in a change in bowel habits. This may include lack of exercise, stress or illness. Constipation can be from medical conditions like irritable bowel syndrome, hormonal abnormalities such as underachieve thyroid, or neuromuscular disorders. Travel can cause constipation. Certain medications can also produce constipation, please see your doctor for further information.

When is Medical Attention Needed?

People should see their doctor for any change in bowel habits or if constipation symptoms are severe, disabling or last longer than three weeks. Bleeding from fissures or hemorrhoids or loss of control of stool should prompt immediate care.

How Can Constipation be managed?

Long-term management of constipation should include healthy lifestyle changes, such as:

- Eating meals on regular schedule
- Increasing fluid and fiber intake
- Chewing food thoroughly
- Exercising
- Not ignoring the urge to have a bowel movement

Your doctor may decide to use MiraLax, an important new prescription product for short-term relief of constipation with predictable results.

Why MiraLax?

MiraLax has a simple once a day dosing and its unique formulation is tasteless and odorless. It is the first new prescription drug therapy for constipation in over 23 years. There is not color or grit. MiraLax is effective in increasing the volume and frequency of bowel movements. It is gentle-acting and well-tolerated.

PATIENT INFORMATION
General

- Patients with constipation should be evaluated for bowel obstruction or metabolic disorders.

- MiraLax should be dissolved in 8 ounces of water to avoid dehydration
- If unusual cramps, nausea, bloating or diarrhea occur, patients should see their doctor.
- Safety and effectiveness in pediatric patients has not been established and it is not known whether MiraLax can cause fetal harm to a pregnant woman, or can effect reproductive capacity. MiraLax should only be given to pregnant women if clearly needed.

MIRALAX™
Polyethylene Glycol 3350, NF Powder

Once-a-day MiraLax sure does the trick,
It makes a normal bowel movement out of a brick.
It bulks up and softens and works on the stool,
It's gentle, it's tasteless, it's easy, it's cool.