

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020698

Trade Name: MiraLax Powder

Generic Name: POLYETHYLENE GLYCOL 3350

Sponsor: BRAINTREE LABORATORIES, INC

Approval Date: 02/18/99

INDICATION(s): FOR OCCASIONAL CONSTIPATION

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020698

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-698

Braintree Laboratories, Inc.
Attention: Mark vB. Cleveland, Ph.D.
60 Columbian Street
P.O. Box 850929
Braintree, MA 02185

FEB 18 1999

Dear Dr. Cleveland:

Please refer to your new drug application (NDA) dated February 26, 1996, received February 28, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MiraLax (polyethylene glycol 3350, NF) Powder.

We acknowledge receipt of your submissions dated December 7, December 14, December 17, 1998, February 8, and February 11, 1999.

This new drug application provides for the use of MiraLax (polyethylene glycol 3350, NF) Powder for occasional constipation.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert, patient package insert, and immediate container labels submitted February 11, 1999). Accordingly, the application is approved effective on the date of this letter.

At the next printing of the labeling, please revise the patient information sheet and the package insert so that they can be separated and the patient information sheet given to the patient.

We remind you of your Phase 4 commitments specified in your submission dated December 17, 1998.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Alice Kacuba, Consumer Safety Officer, at (301) 827-7310.

Sincerely,

/s/

Lilia Talarico, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020698

PRINTED LABELING

BEST POSSIBLE

NDC 52288-900-02


PRESCRIPTION LAXATIVE

MIRALAX


Polyethylene Glycol 3350, NF Powder

This bottle contains
255 grams of polyethylene glycol 3350,
NF powder

Licensed Under U.S. Patent No. 5,710,183



Distributed by
BrainTree
BrainTree, MA 02168



Lot No.:
Exp. Date:

Directions

1. Note: the bottle top is a measuring cap marked to contain 17 grams of powder when filled to the indicated line.
2. Daily dose is 17 g per day or as directed by physician.
3. Pour 17 g (about 1 heaping tablespoon) of powder into the cap of the bottle.
4. Dissolve the powder in a cup (8 oz) of water.
5. Drink the solution.
6. Treatment for 2 to 4 days may be required to produce a bowel movement.

Only
Keep this and other drugs out of reach of children.
Store at 25°C (77°F)

BEST POSSIBLE

255 grams

MiraLax
 Polyethylene Glycol 3350, NF
 Powder

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 $\text{HO}(\text{C}_2\text{H}_4\text{O})_n\text{H}$ 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 effect 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 affect 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 LD₅₀ is >50 gm/kg in mice, rats and rabbits.

255 grams

BEST POSSIBLE

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 28 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

PATIENT INFORMATION

MiraLax® (Polyethylene Glycol 3350, NF Powder) is a prescription only laxative which has been prescribed by your doctor to treat constipation. This product should only be used by the person for whom it was prescribed.

How to take

The dose is 17 grams each day or as directed by physician. It should always be taken by mouth. Measure the dose using the measuring cap (or use one heaping tablespoon of powder), stir and dissolve in a glass (8 oz) of water. Taking more than the prescribed dose may cause loss of fluid due to severe diarrhea.

How will it work

MiraLax softens the stool and increases the frequency of bowel movements by retaining water in the stool. Your first bowel movement will usually happen in two to four days, although results may vary for individual patients.

How long should I take it

MiraLax achieves its best results when used between one and two weeks. You may discontinue taking the drug after you have had several satisfactory bowel movements. Should unusual cramps, bloating, or diarrhea occur, consult your physician. MiraLax is intended for up to a two week course of therapy. You should not use for a longer time unless directed by your doctor.

Next Steps

After successfully completing the MiraLax therapy (usually between one and two weeks) please discuss with your doctor lifestyle changes which may produce more regular bowel habits (adequate dietary and fluid intake, regular exercise).

Who Should NOT take MiraLax

MiraLax should not be used by children. It should not be used by pregnant women unless prescribed by a physician.

Side Effects/Drug Reactions

Occasionally, MiraLax may cause nausea, stomach fullness, cramping, diarrhea and/or gas. Do not take if you have symptoms such as nausea, vomiting, abdominal pain or distention, which may be due to bowel obstruction. On rare occasions hives and skin rashes have been reported which are suggestive of an allergic reaction. If you get an allergic reaction you should discontinue the medication and call your doctor.

If you are allergic to polyethylene glycol, do not use this drug.

BEST POSSIBLE

255 grams

BEST POSSIBLE COPY

NDC 52268-800-03

PRESCRIPTION LAXATIVE

MIRALAX[®]

Polyethylene Glycol 3350, NF Powder

This bottle contains
527 grams of polyethylene glycol 3350,
NF powder

Licensed Under U.S. Patent No. 5,710,183



Distributed by
BrainTree
LABORATORIES, INC
BrainTree, MA 02185



5226880003

Lot No.:
Exp. Date:

Directions

1. Note: the bottle top is a measuring cap marked to contain 17 grams of powder when filled to the indicated line.
2. Daily dose is 17 g per day or as directed by physician.
3. Pour 17 g (about 1 heaping table-spoon) of powder into the cap of the bottle.
4. Dissolve the powder in a cup (8 oz) of water.
5. Drink the solution.
6. Treatment for 2 to 4 days may be required to produce a bowel movement.

TEAR DOWN



5226880003

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BEST POSSIBLE

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527 grams

BEST POSSIBLE COPY