

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-881

LABELING

MoviPrep® (PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride, Sodium Ascorbate and Ascorbic Acid for Oral Solution)

DESCRIPTION

MoviPrep® consists of 4 separate pouches (2 of pouch A and 2 of pouch B) containing white to yellow powder for reconstitution. Each pouch A contains 100 grams of polyethylene glycol (PEG) 3350, NF, 7.5 grams of sodium sulfate, USP, 2.691 grams of sodium chloride, USP, and 1.015 grams of potassium chloride, USP, plus the following excipients: aspartame, NF (sweetener), acesulfame potassium, NF (sweetener), and lemon flavoring. Each pouch B contains 4.7 grams of ascorbic acid, USP and 5.9 grams of sodium ascorbate, USP. When 1 pouch A and 1 pouch B are dissolved together in water to a volume of 1 liter, MoviPrep® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) is an oral solution having a lemon taste.

The entire, reconstituted, 2-liter MoviPrep® colon preparation contains 200 grams of PEG 3350, 15 grams of sodium sulfate, 5.38 grams of sodium chloride, 2.03 grams of potassium chloride, 9.4 grams of ascorbic acid, and 11.8 grams of sodium ascorbate plus the following excipients: aspartame (sweetener), acesulfame potassium (sweetener), and lemon flavoring.

CLINICAL PHARMACOLOGY

MoviPrep® produces a watery stool leading to cleansing of the colon. The osmotic activity of polyethylene glycol 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid, when taken with 1 liter of additional clear fluid, usually results in no net absorption or excretion of ions or water.

The pharmacokinetics of MoviPrep® have not been studied in patients with renal or hepatic insufficiency.

CLINICAL STUDIES

The colon cleansing efficacy and safety of MoviPrep® was evaluated in two randomized, actively-controlled, multi-center, investigator-blinded, phase 3 trials in patients scheduled to have an elective colonoscopy.

In the first study, patients were randomized to one of the following two colon preparation treatments: 1) 2 liters of MoviPrep® with 1 additional liter of clear fluid split into two doses (during the evening before and the morning of the colonoscopy) and 2) 4 liters of polyethylene glycol plus electrolytes solution (4L PEG + E) split into two doses (during the evening before and the morning of the colonoscopy). Patients were allowed to have a morning breakfast, a light lunch, clear soup and/or plain yogurt for dinner. Dinner had to be completed at least one hour prior to initiation of the colon preparation administration.

The primary efficacy endpoint was the proportion of patients with effective colon cleansing as judged by blinded gastroenterologists on the basis of videotapes recorded during the colonoscopy. The blinded gastroenterologists graded the colon cleansing twice (during introduction and withdrawal of the colonoscope) and the poorer of the two assessments was used in the primary efficacy analysis.

The efficacy analysis included 308 adult patients who had an elective colonoscopy. Patients ranged in age from 18 to 88 years old (mean age about 59 years old) with 52% female and 48% male patients. Table 1 displays the results.

Table 1: Effectiveness of Overall Colon Cleansing in the Study of Moviprep® vs 4 Liter Polyethylene Glycol plus Electrolytes Solution

	Responders A ² or B ³ (%)	C ⁴ (%)	D ⁵ (%)
Moviprep® (N=153)	88.9	9.8	1.3
4L PEG + E ¹ (N=155)	94.8	4.5	0.6

¹ 4L PEG + E is 4 Liter Polyethylene Glycol plus Electrolytes Solution

² A: colon empty and clean or presence of clear liquid, but easily removed by suction

³ B: brown liquid or semisolid remaining amounts of stool, fully removable by suction or displaceable, thus allowing a complete visualization of the gut mucosa

⁴ C: semisolid amounts of stool, only partially removable with a risk of incomplete visualization of the gut mucosa

⁵ D: semisolid or solid amounts of stool; consequently colonoscopy incomplete or needed to be terminated.

4 L PEG+E's responder rate was not significantly higher than Moviprep's responder rate.

In the second study, patients were randomized to one of the following two colon preparation treatments:

- 1) 2 liters of Moviprep® with 1 additional liter of clear fluid in the evening prior to the colonoscopy and
- 2) 90 mL of oral sodium phosphate solution (90 mL OSPS) with at least 2 liters of additional clear fluid during the day and evening prior to the colonoscopy. Patients randomized to Moviprep® therapy were allowed to have a morning breakfast, a light lunch, and clear soup and/or plain yogurt for dinner. Dinner had to be completed at least one hour prior to initiation of the colon preparation administration.

The primary efficacy endpoint was the proportion of patients with effective colon cleansing as judged by the colonoscopist and one blinded gastroenterologist (on the basis of videotapes recorded during the colonoscopy). In case of a discrepancy between the colonoscopist and the blinded gastroenterologist, a second blinded gastroenterologist made the final efficacy determination.

The efficacy analysis included 280 adult patients who had an elective colonoscopy. Patients ranged in age from 21 to 76 years old (mean age about 53 years old) with 47% female and 53% male patients. Table 2 displays the results.

Table 2: Effectiveness of Overall Colon Cleansing in the Study of Moviprep® vs 90mL Oral Sodium Phosphate Solution

	Responders A ² or B ³ (%)	C ⁴ (%)	D ⁵ (%)
Moviprep® (N=137)	73.0	23.4	3.6
90 mL OSPS ¹ (N=143)	64.4	29.4	6.3

¹ OSPS is Oral Sodium Phosphate Solution

² A: empty and clean or clear liquid (transparent, yellow, or green)

³ B: brown liquid or semisolid remaining small amounts of stool, fully removable by suction or displaceable allowing a complete visualization of the underlying mucosa

⁴ C: semi solid only partially removable/displaceable stools; risk of incomplete examination of the underlying mucosa

⁵ D: heavy and hard stool making the segment examination uninterpretable and, consequently, the colonoscopy needed to be terminated

MoviPrep's responder rate was not significantly higher than OSPS's responder rate.

INDICATIONS AND USAGE

MoviPrep® is indicated for cleansing of the colon as a preparation for colonoscopy in adults 18 years of age or older.

CONTRAINDICATIONS

MoviPrep® is contraindicated in patients who have had a severe hypersensitivity reaction to any of its components.

WARNINGS

There have been rare reports of generalized tonic-clonic seizures associated with use of polyethylene glycol colon preparation products in patients with no prior history of seizures. The seizure cases were associated with electrolyte abnormalities (e.g., hyponatremia, hypokalemia). The neurologic abnormalities resolved with correction of fluid and electrolyte abnormalities. Therefore, MoviPrep® should be used with caution in patients using concomitant medications that increase the risk of electrolyte abnormalities [such as diuretics or angiotensin converting enzyme (ACE)-inhibitors] or in patients with known or suspected hyponatremia. Consider performing baseline and post-colonoscopy laboratory tests (sodium, potassium, calcium, creatinine, and BUN) in these patients.

MoviPrep® should be used with caution in patients with severe ulcerative colitis, ileus, gastrointestinal obstruction or perforation, gastric retention, toxic colitis, or toxic megacolon.

PRECAUTIONS

General:

Patients with impaired gag reflex and patients prone to regurgitation or aspiration should be observed during the administration of MoviPrep®. If a patient experiences severe bloating, abdominal distention, or abdominal pain, administration should be slowed or temporarily discontinued until the symptoms abate. If gastrointestinal obstruction or perforation is suspected, appropriate tests should be performed to rule out these conditions before administration of MoviPrep®.

Phenylketonurics: MoviPrep® contains phenylalanine – a maximum of 2.33 mg of phenylalanine per treatment.

No additional ingredients (e.g., flavorings) should be added to the MoviPrep® solution.

Since MoviPrep® contains sodium ascorbate and ascorbic acid, MoviPrep® should be used with caution in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency especially G-6-PD deficiency patients with an active infection, with a history of hemolysis, or taking concomitant medications known to precipitate hemolytic reactions.

Information for patients:

MoviPrep® produces a watery stool which cleanses the colon before colonoscopy. It is recommended that patients receiving MoviPrep® be advised to adequately hydrate before, during, and after the use of MoviPrep®. Patients may have clear soup and/or plain yogurt for dinner, finishing the evening meal at least one hour prior to the start of MoviPrep® treatment. No solid food should be taken from the start of MoviPrep® treatment until after the colonoscopy.

The first bowel movement may occur approximately 1 hour after the start of MoviPrep® administration. Abdominal bloating and distention may occur before the first bowel movement. If severe abdominal discomfort or distention occurs, stop drinking temporarily or drink each portion at longer intervals until these symptoms disappear.

Drug Interactions:

Oral medication administered within 1 hour of the start of administration of MoviPrep® may be flushed from the gastrointestinal tract and the medication may not be absorbed.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term studies in animals to evaluate the carcinogenic potential have not been performed with MoviPrep®. Studies to evaluate potential for impairment of fertility or mutagenic potential have not been performed with MoviPrep®.

Pregnancy: Teratogenic Effects:

Pregnancy Category C. Animal reproduction studies have not been performed with MoviPrep®. It is also not known if MoviPrep® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. MoviPrep® should be given to a pregnant woman only if clearly needed.

Nursing Mothers:

Because many drugs are excreted in human milk, caution should be exercised when MoviPrep® is administered to a nursing woman.

Pediatric Use:

The safety and effectiveness of MoviPrep® in pediatric patients has not been established.

Geriatric Use:

Of the 413 patients in clinical studies receiving MoviPrep®, 91 (22%) patients were aged 65 or older, while 25 (6%) patients were over 75 years of age. No overall differences in safety or effectiveness were observed between geriatric patients and younger patients, and other reported clinical experience has not identified differences in responses between geriatric patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

In the MoviPrep® trials, abdominal distension, anal discomfort, thirst, nausea, and abdominal pain were some of the most common adverse reactions to MoviPrep® administration. Since diarrhea was considered as a part of the efficacy of MoviPrep®, diarrhea was not defined as an adverse reaction in the clinical studies. Tables 3 and 4 display the most common drug-related adverse reactions of MoviPrep® and its comparator in the controlled MoviPrep® trials.

Table 3: The Most Common Drug-Related Adverse Reactions¹ (≥ 2%) in the Study of Moviprep® vs. 4 liter Polyethylene Glycol plus Electrolytes Solution

	Moviprep® (split dose) N=180	4L PEG + E ² N=179
	n (%=n/N)	n (%=n/N)
Malaise	35 (19.4)	32 (17.9)
Nausea	26 (14.4)	36 (20.1)
Abdominal pain	24 (13.3)	27 (15.1)
Vomiting	14 (7.8)	23 (12.8)
Upper abdominal pain	10 (5.6)	11 (6.1)
Dyspepsia	5 (2.8)	2 (1.1)

¹ Drug-related adverse reactions were adverse events that were possibly, probably, or definitely related to the study drug.

² 4L PEG + E is 4 liter Polyethylene Glycol plus Electrolytes Solution

Table 4: The Most Common Drug-Related Adverse Reactions¹ (≥ 5%) in the Study of Moviprep® vs. 90 mL Oral Sodium Phosphate Solution

	Moviprep® (evening-only) (full dose) N=169	90 mL OSPS ² N=171
	n (%=n/N)	n (%=n/N)
Abdominal distension	101 (59.8)	70 (40.9)
Anal discomfort	87 (51.5)	89 (52.0)
Thirst	80 (47.3)	112 (65.5)
Nausea	80 (47.3)	80 (46.8)
Abdominal pain	66 (39.1)	55 (32.2)
Sleep disorder	59 (34.9)	49 (28.7)
Rigors	57 (33.7)	51 (29.8)
Hunger	51 (30.2)	121 (70.8)
Malaise	45 (26.6)	90 (52.6)
Vomiting	12 (7.1)	14 (8.2)
Dizziness	11 (6.5)	31 (18.1)
Headache	3 (1.8)	9 (5.3)
Hypokalemia	0 (0)	10 (5.8)
Hyperphosphatemia	0 (0)	10 (5.8)

¹ Drug-related adverse reactions were adverse events that were possibly, probably, or definitely related to the study drug. In addition to the recording of spontaneous adverse events, patients were also specifically asked about the occurrence of the following symptoms: shivering, anal irritations, abdominal bloating or fullness, sleep loss, nausea, vomiting, weakness, hunger sensation, abdominal cramps or pain, thirst sensation, and dizziness.

² OSPS is Oral Sodium Phosphate Solution

Isolated cases of urticaria, rhinorrhea, dermatitis, and anaphylactic reaction have been reported with PEG-based products and may represent allergic reactions.

Published literature contains isolated reports of serious adverse events following the administration of PEG-based products in patients over 60 years of age. These adverse events included upper gastrointestinal bleeding from a Mallory-Weiss tear, esophageal perforation, asystole, and acute pulmonary edema after aspirating the PEG-based preparation.

OVERDOSAGE

There have been no reported cases of overdose with Moviprep®. Purposeful or gross accidental ingestion of more than the recommended dose of Moviprep® might be expected to lead to severe electrolyte disturbances, including hyponatremia and/or hypokalemia, as well as dehydration and hypovolemia, with signs and symptoms of these disturbances. The patient who has taken an overdose should be monitored carefully, and treated symptomatically for complications until stable.

DOSAGE AND ADMINISTRATION

The Moviprep® dose for colon cleansing for adult patients is 2 liters (approximately 64 ounces) of Moviprep® solution (with 1 additional liter of clear fluids) taken orally prior to the colonoscopy in one of the following ways:

- 1) **Split-dose Moviprep® regimen:** The evening before the colonoscopy, take the first liter of Moviprep® solution over one hour (one 8 ounce glass every 15 minutes) and then drink 0.5 liters (approximately 16 ounces) of clear fluid. Then, on the morning of the colonoscopy, take the second liter of Moviprep® solution over one hour and then drink 0.5 liters of clear liquid at least one hour prior to the start of the colonoscopy; or
- 2) **Evening-only (Full-dose) Moviprep® regimen:** Around 6 PM in the evening before the colonoscopy, take the first liter of Moviprep® solution over one hour (one 8 ounce glass every 15 minutes) and then about 1.5 hours later take the second liter of Moviprep® solution over one hour. In addition, take 1 liter (approximately 32 ounces) of additional clear liquid during the evening before the colonoscopy.

Preparation of the Moviprep® solution:

Moviprep® solution is prepared by emptying the contents of 1 pouch A and 1 pouch B into a suitable glass container (or the container provided) and adding to the container 1 liter of lukewarm water. Mix the solution to ensure that the ingredients are completely dissolved. If the patient prefers, the Moviprep® solution can be refrigerated prior to drinking. The reconstituted solution should be used within 24 hours.

After consumption of the first liter of Moviprep® solution, the above mixing procedure should be repeated with the second pouch A and pouch B to reconstitute the second liter of the Moviprep® solution.

HOW SUPPLIED

Moviprep® is supplied in powdered form. Moviprep® is administered as an oral solution after reconstitution.

MoviPrep® is available in the following presentations:

Carton: The MoviPrep® carton contains a disposable container for reconstitution of MoviPrep® and an inner carton containing 4 pouches (2 of pouch A and 2 of pouch B). Pouch A contains polyethylene glycol (PEG) 3350 100 grams, sodium sulfate 7.5 grams, sodium chloride 2.69 grams, and potassium chloride 1.015 grams. Pouch B contains ascorbic acid 4.7 grams and sodium ascorbate 5.9 grams. 1 pouch A and 1 pouch B should be dissolved together in 1 liter of lukewarm water. When reconstituted to 1 liter volume with water, the solution contains PEG-3350 29.6 mmol/L, sodium 181.6 mmol/L (of which not more than 56.2 mmol is absorbable), sulfate 52.8 mmol/L, chloride 59.8 mmol/L, potassium 14.2 mmol/L, and ascorbate 29.8 mmol/L.

NDC 65649-201-75

Rx only

STORAGE

Store carton/container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). When reconstituted, store upright and keep solution refrigerated. Use within 24 hours.

Manufactured by:

Norgine B.V.

Harefield, Uxbridge, Middelsex UB9 6NS

United Kingdom

For:

Salix Pharmaceuticals, Inc.

Morrisville, NC 27560

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Submitted
8/2/06

NDC 65649-201-75

Rx only

MoviPrep®

(PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride,
Sodium Ascorbate and Ascorbic Acid for Oral Solution)

On reconstitution in one liter of water, one Pouch A
and one Pouch B provide:

PEG-3350	29.6 mmol/L
Sodium	181.6 mmol/L
Chloride	59.8 mmol/L
Sulfate	52.8 mmol/L
Potassium	14.2 mmol/L
Ascorbate	29.8 mmol/L

Container for reconstitution of MoviPrep®

Directions for use:

Dissolve the contents of one Pouch **A** and one Pouch **B** in one liter of water and drink one 8 oz glass of the solution (approximately 240 mL) every 15-30 minutes until gone, followed by 16 oz of clear fluid (approximately 500 mL). Repeat as directed.

Important:

See package insert for full prescribing information.

When reconstituted, store upright and keep solution refrigerated. Use within 24 hours.

Keep out of the reach of children.

Phenylketonurics: contains phenylalanine – a maximum of 2.33 mg per course of treatment

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MoviPrep

(PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride, Sodium Ascorbate and Ascorbic Acid for Oral Solution)

PATIENT INSTRUCTIONS - See inside for full Prescribing Information.

- Step 1** The MoviPrep® carton contains a disposable container for reconstitution of MoviPrep® and an inner carton containing 4 Pouches (2 x Pouch A and 2 x Pouch B). Take 1 Pouch A and 1 Pouch B (empty) and contents into the disposable container. Add 1 liter of lukewarm drinking water.
- Step 2** Mix to dissolve. Do not add any other ingredients, flavors, etc. If the patient prefers the solution may be refrigerated before drinking. Keep the reconstituted solution in an upright position. Use within 24 hours.

MoviPrep® solution is taken orally in one of the following ways:

Split-dose MoviPrep® regimen: The evening before the colonoscopy, take the first liter of MoviPrep® solution over one hour (one 8 ounce glass every 15 minutes) and then drink 0.5 liters (approximately 16 ounces) of clear fluid. Then, on the morning of the colonoscopy, take the second liter of MoviPrep® solution over one hour and then drink 0.5 liters of clear fluid at least one hour prior to the start of the colonoscopy.

OR

Evening-only (full-dose) MoviPrep® regimen: Around 6 pm in the evening before the colonoscopy, take the first liter of MoviPrep® solution over one hour (one 8 ounce glass every 15 minutes) and then about 1.5 hours later, take the second liter of MoviPrep® solution over one hour. In addition, take 1 liter (approximately 32 ounces) of additional clear fluid over the evening before the colonoscopy.

A loose watery stool may occur during the first hour after the start of MoviPrep® administration.

No solid food should be eaten from the start of the MoviPrep® treatment until after the colonoscopy.

Storage Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

Keep out of the reach
of children.

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Moviprep[®]

(PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride,
Sodium Ascorbate and Ascorbic Acid for Oral Solution)

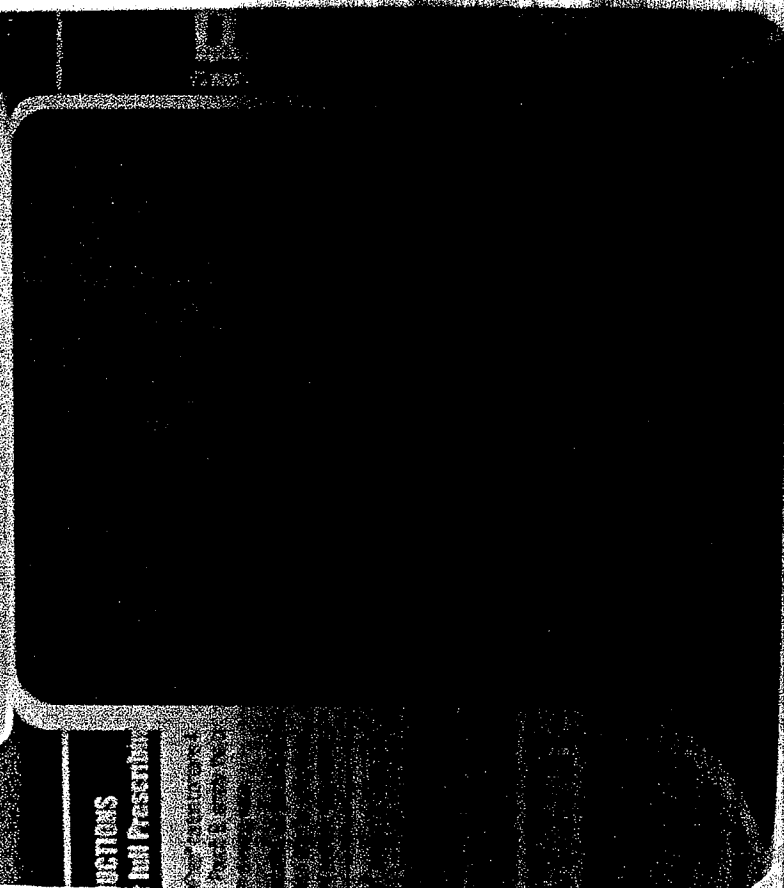
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ADA 19-201-75

Moviprep

(PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride, Sodium Ascorbate and Aspartic Acid for Oral Solution)

Rx only



Phenylalanine:
contains phenylalanine—
a maximum of 2.33 mg
per course of treatment.

CAUTIONS
Full Prescriber
See Instructions
Pack 8, 9 and 10

This carton contains
One container for reconstitution of 100 g

2 x Pouch A		Each Pouch A contains:		Per 100 g	
PEG-3350	100 g	Ascorbic acid	200 mg	PEG-3350	29.6 mmol/L
Sodium sulfate	7.5 g	Sodium chloride	600 mg	Sodium Chloride	361.6 mmol/L
Sodium chloride	2.691 g			Sulfate	59.6 mmol/L
Potassium chloride	1.015 g			Potassium Chloride	14.2 mmol/L
also contains aspartame				Aspartic Acid	20.8 mmol/L

MoviPrep

MoviPrep
(PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride,
Sodium Ascorbate and Ascorbic Acid for Oral Solution)

PATIENT INSTRUCTIONS - See inside or full prescribing information.

The MoviPrep[®] carton contains a disposable container for reconstitution of MoviPrep[®] and an inner carton containing 4 Pouches (2 x Pouch A and 2 x Pouch B). Take 1 Pouch A and 1 Pouch B, empty the contents into the disposable container. Add 1 liter of lukewarm drinking water.

Was to dissolve. Do not add any other ingredients, flavors, etc. If the patient creates the solution, mix, or refrigerated before drinking, keep the reconstituted solution at 2-8°C (36-46°F) condition, 359 within 24 hours.

MoviPrep[®] solution is taken orally in one of the following ways:
Split-dose MoviPrep[®] regimen: The evening before the colonoscopy, take the first liter of MoviPrep[®] solution over one hour (one 8 ounce glass every 15 minutes) and then drink 16.5 liters (approximately 16 ounces) of clear fluid. Then, on the morning of the colonoscopy, take the second liter of MoviPrep[®] solution over one hour and then drink 16.5 liters of clear fluid at least one hour prior to the start of the colonoscopy.

OR
Evening-only (full-dose) MoviPrep[®] regimen: Remove 16.5 liters of the solution before the colonoscopy, take the first liter of MoviPrep[®] solution over one hour (one 8 ounce glass every 15 minutes) and then about 1.5 hours later take the second liter of MoviPrep[®] solution over one hour. In addition, take 1 liter (approximately 32 ounces) of additional clear fluid during the evening before the colonoscopy.

A loose, watery bowel movement may result, in approximately one hour after the start of MoviPrep[®] administration.
No solid food should be taken from the start of the MoviPrep[®] treatment until after the colonoscopy.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

See full prescribing information for complete information.

NDC 66649-201-75

MoviPrep

(PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride,
Sodium Ascorbate and Ascorbic Acid for Oral Solution)



Rx only

Pharmaceuticals
A Salix Company
per Carton of Product

Net Content: 16.5 L (4.4 gal) of Oral Solution

PEG-3350	100 g
Sodium Sulfate	2,100 g
Potassium Chloride	1,015 g
Also contains ascorbate	

PEG-3350	4.7 g
Ascorbic acid	5.9 g
Sodium sulfate	71.6 mmol
Sodium chloride	2.8 mmol
Potassium chloride	1.4 mmol
Also contains ascorbate	

PEG-3350	29.6 mmol
Sodium sulfate	91.6 mmol
Sodium chloride	3.4 mmol
Potassium chloride	1.7 mmol
Also contains ascorbate	

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MoviPrep
(PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride,
Sodium Ascorbate and Ascorbic Acid for Oral Solution)



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