PRODUCT MONOGRAPH

MOVIPREP®

Macrogol 3350, Sodium sulphate anhydrous, Sodium chloride, Potassium chloride, Ascorbic acid, Sodium ascorbate

Powder for oral solution

Sachet A	
Macrogol (Polyethylene glycol) 3350	*100 g*
Sodium sulphate anhydrous	*7.5 g*
Sodium chloride	*2.691 g*
Potassium chloride	*1.015 g*
Sachet B	
Ascorbic acid	*4.7 g*
Sodium ascorbate	*5.9 g*

Osmotic Laxative

Aralez Pharmaceuticals Canada Inc.
6733 Mississauga Road, Suite 800
Mississauga, ON, Canada
L5N 6J5

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MOVIPREP®

(Macrogol 3350, Sodium sulphate anhydrous, Sodium chloride, Potassium chloride, Ascorbic acid, Sodium ascorbate)

Powder for oral solution in sachets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Powder for oral solution per Sachet A: *Macrogol 3350* *100g* *Sodium Sulphate Anhydrous* *7.5g* *Sodium Chloride* *2.691g* *Potassium Chloride* *1.015g* Sachet B: *Ascorbic Acid* *4.7g* *Sodium Ascorbate* *5.9g* *Note:* MOVIPREP consists of 4 separate pouches (2 of Sachet A and 2 of Sachet B).	Aspartame (E951), Acesulfame Potassium (E950), Lemon flavor (containing maltodextrin, citral, lemon oil, lime oil, xanthan gum, vitamin E). *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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

Geriatrics (65 up to 85 years of age):
No overall differences in safety or effectiveness have been observed between geriatric and younger patients. However, greater sensitivity of some older individuals cannot be ruled out (see **WARNINGS AND PRECAUTIONS - Special Populations, Geriatrics** and **ADVERSE REACTIONS**).

Pediatrics (< 18 years of age):
Not recommended for use in children below 18 years of age, as MOVIPREP has not been studied in the pediatric population (see **WARNINGS AND PRECAUTIONS - Special Populations, Pediatrics** and **ADVERSE REACTIONS**).

CONTRAINDICATIONS

- MOVIPREP is contraindicated in patients with known hypersensitivity to this drug or to any ingredient in the formulation or component of the container (see **WARNINGS AND PRECAUTIONS – Immune**). For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

- Do not use in patients with known or suspected:
    - Gastrointestinal obstruction or perforation
    - Disorders of gastric emptying (e.g. gastroparesis)
    - Ileus
    - Toxic megacolon which complicates severe inflammatory conditions of the intestinal tract including Crohn's disease and ulcerative colitis
    - Toxic colitis
    - Acute surgical abdominal conditions such as acute appendicitis and diverticulitis

- Do not use in unconscious patients.

WARNINGS AND PRECAUTIONS

General

Caution should be used in the administration of MOVIPREP to frail or debilitated patients.

MOVIPREP should be used with caution in patients with:

- Impaired gag reflex, with the possibility of regurgitation or aspiration
- Impaired consciousness
- Renal impairment whose creatinine clearance is less than 30 mls/minute
- Grade III or IV cardiac failure
- Dehydration
- Severe acute inflammatory bowel disease

The presence of dehydration should be corrected before the use of MOVIPREP.

MOVIPREP contains aspartame (a source of phenylalanine), which may be harmful for people with phenylketonuria.

In debilitated fragile patients, patients with poor health, those with clinically significant renal impairment and those at risk of electrolyte imbalance, the physician should consider performing a baseline and post-treatment electrolyte and renal function test (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Test**).

If patients develop any symptoms indicating shifts of fluid/electrolytes (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma electrolytes should be measured and any abnormality treated appropriately (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Test**).

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

MOVIPREP may result in a potential interactive effect when used with starch-based food thickeners. The polyethylene glycol (PEG) ingredient counteracts the thickening effect of starch, effectively liquefying preparations that need to remain thick for people with swallowing problems. This warning applies to all PEG-containing products.

Ascorbic acid:
Patients with Glucose-6-phosphate dehydrogenase deficiency may be at risk of acute haemolysis due to the presence of ascorbate.

About 5% of individuals develop hyperoxalutia after large doses of ascorbic acid. Ascorbic acid may cause acidification of the urine, occasionally leading to precipitation of urate, cymbal, or oxalate stones, or drugs in the urinary tract. Large doses of ascorbic acid should be avoided in patients with hyperosaluria.

Uric acid excretion may be increased by ascorbic acid. Theoretically, large doses of ascorbic acid could result in gouty arthritis in susceptible individuals.

Rarely, decreased blood pH leading to sickle-cell crisis has been reported in patients with sickle-cell disease after large doses of ascorbic acid.

Deep-vein thrombosis has reportedly occurred after large doses of ascorbic acid.

Very high doses of ascorbic acid might possibly interfere with glucose determinations.

High doses of ascorbic acid may increase iron absorption. Caution is advised in hemochromatosis, sideroblastic anemia, or thalassemia.

Carcinogenesis and Mutagenesis
Long-term studies in animals to determine the carcinogenic potential of MOVIPREP have not been performed (see **TOXICOLOGY)**.

Cardiac Arrhythmias

There have been rare reports of serious cardiac arrhythmias associated with the use of ionic osmotic laxative products for bowel preparation. Use caution when prescribing MOVIPREP for patients at increased risk of arrhythmias (e.g., patients with a history of prolonged QT, uncontrolled arrhythmias, recent myocardial infarction, unstable angina, congestive heart failure, or cardiomyopathy). Pre-dose and post-colonoscopy ECGs should be considered in patients at increased risk of serious cardiac arrhythmias.

Gastrointestinal

Use of MOVIPREP is not recommended when abdominal pain, nausea, or vomiting are present.

Semi-conscious patients, patients with impaired gag reflex or patients prone to aspiration or regurgitation should be closely observed during administration of MOVIPREP, especially if this is via a nasogastric route.

If gastrointestinal obstruction or perforation is suspected, appropriate tests should be performed to rule out these conditions before administration of MOVIPREP.

If a patient experiences severe bloating, abdominal distension, abdominal pain or any other reaction which makes it difficult to continue the preparation, administration should be slowed or temporarily discontinued until the symptoms abate.

Immune

Anaphylaxis and Hypersensitivity:

As with other macrogol (polyethylene glycol, PEG) containing products, allergic reactions including rash, urticaria, pruritus, angioedema and anaphylaxis are a possibility (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

Neurologic

There have been reports of generalized tonic-clonic seizures associated with use of macrogol (PEG) colon preparation products in patients with no prior history of seizures. The seizure cases were associated with electrolyte abnormalities (e.g., hyponatremia, hypokalemia) as well as severe vomiting and excessive beverage consumption. 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 [e.g., diuretics or angiotensin converting enzyme (ACE)-inhibitors] or in patients with known or suspected hyponatremia. Monitor baseline and post-colonoscopy laboratory tests (sodium, potassium, calcium, creatinine, and BUN) in these patients (see **WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests**).

Renal

Patients with impaired water handling who experience severe vomiting should be closely monitored, including measurement of electrolytes (sodium, potassium, calcium, BUN and creatinine) (see **WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests**).

Special Populations

Pregnant Women: There are no data on the use of MOVIPREP during pregnancy and it should only be used if considered essential by the physician.

Animal reproduction studies have not been performed with MOVIPREP (see **TOXICOLOGY**). Ingestion of large doses of ascorbic acid during pregnancy has resulted in scurvy in neonates.

Nursing Women: No data is available regarding the excretion of the active ingredients of MOVIPREP in human milk. It is therefore not recommended to use MOVIPREP while nursing.

Pediatrics (< 18 years of age): Not recommended for use in children below 18 years of age, as MOVIPREP has not been studied in the pediatric population.

Geriatrics (65 up to 85 years of age): No overall differences in safety or effectiveness were observed between geriatric patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. Potentially serious complications may arise if abnormal fluid intake or losses occur simultaneously in this sub-population. Suboptimal oral intake of water and electrolytes could create clinically significant deficiencies in less fit patients, in particular elderly, debilitated and patients at risk of hypokalaemia.

Published literature contains 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 (see **ADVERSE REACTIONS**).

Monitoring and Laboratory Tests

In debilitated fragile patients, patients with poor health, those with clinically significant renal impairment and those at risk of electrolyte imbalance, the physician should consider performing a baseline and post-treatment electrolyte and renal function test (see **WARNINGS AND PRECAUTIONS** – **General**, **Neurologic**, **Renal**).

If patients develop any symptoms indicating shifts of fluid/electrolytes (e.g. oedema, shortness of breath, increasing fatigue, cardiac failure), plasma electrolytes should be measured and any abnormality treated appropriately (see **WARNINGS AND PRECAUTIONS** – **General**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The majority of adverse events across all studies was related to gastrointestinal disturbances such as among others abdominal pain, nausea, anal discomfort. Other commonly reported adverse events during the clinical studies were malaise and headache. Most adverse events were mild to moderate in severity and transient. In Phase III studies, discontinuation due to a possibly related treatment-emergent adverse event occurred in

2.87% of MOVIPREP treated patients.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 1 and 2 display the most common drug-related adverse reactions (≥1%) of MOVIPREP and its comparators in the MOVIPREP trials.

Table 1: The Most Common Drug-Related Adverse Reactions[1] (≥1%) Observed in Adult Patients Treated with MOVIPREP Split-Dose or Comparator Treatment in Clinical Studies – ITT Population[2]

System Organ Class / Preferred Term	MOVIPREP Split-Dose[3] N = 180 n (% = n/N)	Comparator[4] N = 179 n (%= n/N)
Total number of drug-related AE(s)[1,5]	114	131
Total number (%) of subjects with drug-related AE(s)[1,5]	69 (38.3)	75 (41.9)
Gastrointestinal Disorders		
Nausea	26 (14.4)	36 (20.1)
Abdominal pain NOS[6]	24 (13.3)	27 (15.1)
Vomiting NOS[6]	14 (7.8)	23 (12.8)
Abdominal pain upper	10 (5.6)	11 (6.1)
Dyspepsia	5 (2.8)	2 (1.1)
General Disorders and Administration Site Conditions		
Malaise	35 (19.4)	32 (17.9)

[1] Drug-related adverse reactions were adverse events that were possibly, probably, or definitely related to the study drug.
[2] ITT: The Intent-to-Treat (ITT) population includes all randomised patients who received at least some of the investigational product.
[3] Split-dose: Split into two doses (during the evening before and the morning of the colonoscopy).

[4] Comparator was 4 Litre Polyethylene Glycol plus Electrolytes Solution (4L PEG + E).
[5] AE(s): Adverse Events.
[6] NOS: Not otherwise specified.

Table 2: The Most Common Drug-Related Adverse Reactions[1] (≥1%) Observed in Adult Patients Treated with MOVIPREP Full-Dose (Evening Only) or Comparator Treatment in Clinical Studies – ITT Population[2]

System Organ Class / Preferred Term	MOVIPREP Full-Dose (Evening Only)[3] N = 169 n (%= n/N)	Comparator[4] N = 171 n (%= n/N)
Total number of drug-related AE(s)[1,5]	654	791
Total number (%) of subjects with drug-related AE(s)[1,5]	160 (94.7)	160 (93.6)
Gastrointestinal Disorders		
Abdominal distension	101 (59.8)	70 (40.9)
Anal discomfort	87 (51.5)	89 (52.0)
Nausea	80 (47.3)	80 (46.8)
Abdominal pain NOS[6]	66 (39.1)	55 (32.2)
Vomiting NOS[6]	12 (7.1)	14 (8.2)
Dysphagia	2 (1.2)	0 (0.0)
General Disorders and Administration Site Conditions		
Thirst	80 (47.3)	112 (65.5)
Rigors	57 (33.7)	51 (29.8)
Malaise	45 (26.6)	90 (52.6)
Metabolism and Nutrition Disorders		
Hunger	51 (30.2)	121 (70.8)
Hypokalaemia	0 (0.0)	10 (5.8)
Hyperphosphatemia	0 (0.0)	10 (5.8)
Nervous System Disorder		
Dizziness	11 (6.5)	31 (18.1)
Headache	3 (1.8)	9 (5.3)
Psychiatric Disorders		

Sleep disorder NOS[6]	59 (34.9)	49 (28.7)

[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] ITT: The Intent-to-Treat (ITT) population includes all randomised patients who received at least some of the investigational product.
[3] Full-dose: Only in the evening prior to the colonoscopy.
[4] Comparator was Oral Sodium Phosphate Solution (OSPS).
[5] AE(s): Adverse Events.
[6] NOS: Not otherwise specified.

Cases of urticaria, rhinorrhea, dermatitis, and anaphylactic reactions have been reported with macrogol (PEG)-based products which may represent allergic reactions (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS** – **Immune**).

Published literature contains reports of serious adverse events following the administration of macrogol (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 macrogol (PEG)-based preparation (see **INDICATIONS AND CLINICAL USE** and **WARNINGS AND PRECAUTIONS** – **Special Populations**, **Geriatrics**).

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Treatment-related adverse events (possibly, probably or definitely related) reported in less than (<) 1.0% of patients treated with MOVIPREP included:

Blood and Lymphatic System Disorders: leucopenia.

Cardiac and Vascular Disorders: angina pectoris, hot flushes.

Gastrointestinal Disorders: dry mouth, flatulence, intestinal spasm, bowel sounds abnormal, constipation, dysphagia, proctalgia, hypoesthesia oral, irritable bowel syndrome.

General Disorders and Administration Site Conditions: discomfort.

Investigations: blood bicarbonate decreased, abnormal liver function tests.

Metabolism and Nutrition Disorders: hypophosphataemia.

Nervous System Disorders: dysgeusia, formication.

Respiratory, Mediastinal and Thoracic Disorders: nasopharyngitis.

Skin and Subcutaneous Tissue Disorders: pruritus, allergic dermatitis.

Abnormal Hematologic and Clinical Chemistry Findings

No significant changes in laboratory parameters were observed in the clinical trials conducted.

Post-Market Adverse Drug Reactions

The following drug-related adverse reactions were reported by post-marketing experience. Because post-market adverse events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Cardiac Disorders: transient increase in blood pressure.

Gastrointestinal Disorders: nausea, vomiting, abdominal pain, abdominal distension, anal discomfort, dyspepsia, flatulence, retching.

General Disorders and Administration Site Conditions: rigors, thirst, malaise, hunger.

Immune System Disorders: allergic reactions, anaphylaxis, angioedema.

Investigations: electrolytes disturbances including blood bicarbonate decreased, hypokalaemia, hyper and hypocalcaemia, hypophosphataemia, hyponatraemia (occurs more commonly in patients taking concomitant medication affecting the kidneys such as ACE inhibitors and diuretics) and changes in the blood chloride levels.

Nervous System Disorders: headache, dizziness. Convulsions associated with severe hyponatraemia.

Skin and Subcutaneous Tissue Disorders: rash, pruritus, urticaria.

DRUG INTERACTIONS

Overview

No drug interaction studies were conducted with MOVIPREP. MOVIPREP should be used with caution in patients using concomitant medications that increase the risk of electrolyte abnormalities (see **DRUG INTERACTIONS** – **Drug-Drug Interactions**).

Drug-Drug Interactions

No drug-drug interaction studies were conducted with MOVIPREP.

MOVIPREP should be used with caution in patients using concomitant medications that increase the risk of electrolyte abnormalities [e.g., diuretics or angiotensin converting

enzyme (ACE)-inhibitors].

Oral medication should not be taken within one hour of administration of MOVIPREP as it may be flushed from the gastro-intestinal tract and not absorbed.

The literature indicates that large doses of ascorbic acid (1g vitamin C daily) increases the plasma concentration of ethinyloestradiol in women taking oral contraceptives, and this is followed by heavy breakthrough vaginal bleeding when vitamin C is stopped. It is not known whether this has an effect on contraceptive efficacy (see **DETAILED PHARMACOLOGY**).

Acidification of the urine following administration of ascorbic acid may result in altered excretion of other drugs. For instance, large doses of ascorbic acid may lower urinary pH and cause renal tubular reabsorption of acidic medications with concurrent administration; alkaline medications may exhibit decreased reabsorption.

Drug-Food Interactions
No solid food should be taken from the start of MOVIPREP treatment until after the clinical procedure.

Patients should adequately hydrate before, during, and after the use of MOVIPREP.

It is strongly recommended that one litre of clear liquid, which may include water, clear soup, fruit juice without pulp, soft drinks, tea and/or coffee without milk, is also taken during the course of treatment.

Drug-Herb Interactions
Interactions of MOVIPREP with herbal products have not been established.

Drug-Laboratory Interactions
Interactions of MOVIPREP with laboratory tests have not been established.

Because ascorbic acid is a strong reducing agent, it interferes with laboratory tests based on oxidation-reduction reactions. Specialized references should be consulted for specific information on laboratory test interferences caused by ascorbic acid.

Drug-Lifestyle Interactions
Interactions of MOVIPREP with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

To prevent the development of dehydration it is recommended to drink 1.0 litre of water in

addition to the preparation.

In clinical practice the choice of MOVIPREP treatment intake may be based on the timing of the colonoscopy procedure and patient preference.

Recommended Dose and Dosage Adjustment

Adults aged 18 years or older: A course of treatment consists of two litres of MOVIPREP. It is strongly recommended that one litre of clear liquid, which may include water, clear soup, fruit juice without pulp, soft drinks, tea and/or coffee without milk, is also taken during the course of treatment.

A litre of MOVIPREP consists of one 'Sachet A' and one 'Sachet B' dissolved together in one litre of water. This reconstituted solution should be drunk over a period of one to two hours. This should be repeated with a second litre of MOVIPREP.

This course of treatment can be taken:

1) **Split-dose MOVIPREP regimen:** The evening before the colonoscopy, take the first litre of MOVIPREP solution over one hour (one 8 ounce glass every 15 minutes) and then drink 0.5 litres (approximately 16 ounces) of clear fluid. Then, on the morning of the colonoscopy, take the second litre of MOVIPREP solution over one hour and then drink 0.5 litres of clear liquid at least one hour prior to the start of the colonoscopy; or

2) **Full-dose (Evening-only) MOVIPREP regimen:** Around 6 PM in the evening before the colonoscopy, take the first litre of MOVIPREP solution over one hour (one 8 ounce glass every 15 minutes) and then about 1.5 hours later take the second litre of MOVIPREP solution over one hour. In addition, take 1 litre (approximately 32 ounces) of additional clear liquid during the evening before the colonoscopy.

There should be at least one hour between the end of intake of fluid (MOVIPREP or clear liquid) and the start of colonoscopy.

No solid food should be taken from the start of the course of treatment until after the clinical procedure.

Pediatrics: Not recommended for use in children below 18 years of age, as MOVIPREP has not been studied in the pediatric population.

Missed Dose

If the MOVIPREP dose is missed by a few hours, MOVIPREP should be taken as soon as possible. If several hours have passed since the time when the dose should have been taken, the dosage schedule should be based on the clinical judgment of the physician. It is important that the preparation be completed at least an hour before the procedure.

Administration

MOVIPREP is in powder dosage form and is reconstituted for oral use (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

Visually inspect the solution prior to use. Do not use if discolored or if particles are present.

Reconstitution:

MOVIPREP consists of 4 separate pouches (2 of Sachet A and 2 of Sachet B) containing white to yellow powder for reconstitution.

MOVIPREP pack contains 2 clear bags each containing one pair of sachets: Sachet A and Sachet B. Each pair of sachets (A and B) is to be dissolved in water to make a one litre of solution. This pack is therefore sufficient to make up to 2 litres of MOVIPREP solution.

MOVIPREP solution is prepared by emptying the contents of 1 Sachet A and 1 Sachet B into a suitable glass container (or the container provided) and adding to the container 1 litre of 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. Discard unused portion.

After consumption of the first litre of MOVIPREP solution, the above mixing procedure should be repeated with the second Sachet A and Sachet B to reconstitute the second litre of the MOVIPREP solution.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Gross overdosage may cause severe diarrhea, severe electrolyte disturbances, including hyponatremia and/or hypokalemia, as well as dehydration and hypovolemia, with signs and symptoms of these disturbances.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MOVIPREP is a macrogol (polyethylene glycol, PEG)-based bowel cleansing agent intended for use as a preparation for colonoscopy. Its clinical efficacy derives from the

osmotic action of macrogol (PEG) 3350, sodium sulphate, ascorbic acid and sodium ascorbate acting in concert. Due to the sequestration of water by macrogol (PEG), these ingredients exert a synergistic action, increasing the final osmolality to levels greater than would be theoretically calculated from the individual components. As a result, the patient needs only to ingest half the volume (2L instead of 4L) normally required for adequate bowel cleansing with other products. In addition to these ingredients, sodium ascorbate, sodium chloride and potassium chloride maintain electrolyte balance while aspartame, acesulfame potassium and a lemon flavoring agent improve palatability. The product is palatable such that the required osmotic load can be ingested in half the volume, but for safety an extra litre of water or clear fluid must be taken concurrently to balance the water loss.

Pharmacodynamics

MOVIPREP produces a watery stool leading to cleansing of the colon.

Macrogol (PEG) 3350, sodium sulphate and high doses of ascorbic acid exert an osmotic action in the gut, which induce a laxative effect. Macrogol (PEG) 3350 increases the stool volume, which stimulates colon motility via neuromuscular pathways. The physiological consequence is a propulsive colonic transportation of the softened stools.

The electrolytes present in the formulation as well as the supplementary clear liquid intake are included to prevent clinically significant variations of sodium, potassium or water, and thus reduce dehydration risk.

Pharmacokinetics

Macrogol (PEG) 3350 is unchanged along the gut. It is virtually unabsorbed from the gastro-intestinal tract. Any macrogol (PEG) 3350 that is absorbed is excreted via the urine.

Ascorbic acid is absorbed mainly at the small intestine level by a mechanism of active transport, which is sodium dependent and saturable. There is an inverse relationship between the ingested dose and the percentage of the absorbed dose. For oral doses between 30 and 180 mg an amount of about 70-85 % of the dose is absorbed. Following oral intake of up to 12 g ascorbic acid, it is known that only 2 g is absorbed.

After high oral doses of ascorbic acid and when plasma concentrations exceed 14 mg/litre, the absorbed ascorbic acid is mainly eliminated unchanged in the urine.

Special Populations and Conditions

The pharmacokinetics of MOVIPREP has not been studied in special populations (e.g., pediatrics, geriatrics, gender, race, genetic polymorphism) or certain conditions (e.g., hepatic insufficiency, renal insufficiency).

STORAGE AND STABILITY

Sachets: Store at temperature 5°C -25°C. Store in the original package.

Reconstituted Solution: Store at temperature 15°C-25°C. The solution may be refrigerated (2°C -8°C). Keep the solution covered. Discard unused portion.

Shelf life:

Sachets	3 years
Reconstituted solution	24 hours

SPECIAL HANDLING INSTRUCTIONS

Reconstitution of MOVIPREP in water may take up to 5 minutes and is best performed by adding the powder to the mixing vessel first followed by the water. The patient should wait until all the powder has dissolved before drinking the solution.

After reconstitution in water, MOVIPREP consumption may begin immediately or if preferred it may be cooled before use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Powder for oral solution.

Free flowing white to yellow powder in Sachet A.
Free flowing white to light brown powder in Sachet B.

Sachet A contains the following active substances:

Macrogol (PEG) 3350	100 g
Sodium sulphate anhydrous	7.500 g
Sodium chloride	2.691 g
Potassium chloride	1.015 g

Sachet B contains the following active substances:

Ascorbic acid	4.700 g
Sodium ascorbate	5.900 g

MOVIPREP powder for oral solution contains the following non-medicinal ingredients: acesulfame potassium (E950) as sweeteners, aspartame (E951) and lemon flavouring (containing citral, lemon oil, lime oil, maltodextrin, vitamin E, xanthan gum).

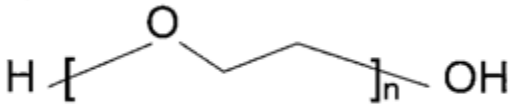
A paper / low density polyethylene / aluminium / low density polyethylene sachet containing 112 g of white powder (‘Sachet A’) and a paper / low density polyethylene / aluminium / low density polyethylene sachet containing 11 g of white powder (‘Sachet B’).
Both sachets are contained in a transparent bag.
One pack of MOVIPREP contains a single treatment of two transparent bags.
Pack sizes of 1 pack of a single treatment.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

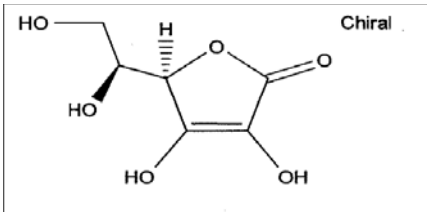
Drug Substance

1) Macrogols

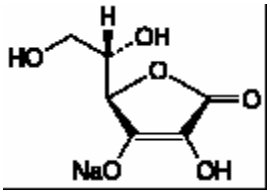
Proper name:	Macrogols
Chemical name:	Polyethylene glycol
Molecular formula and molecular mass:	$H(C_2H_4O)_nOH$, 3350 (n=76)
Structural formula:	$HOCH_2 – (CH_2 - O – CH_2)_n – CH_2OH$ 
Empirical Formula:	$HOCH_2(CH_2OCH_2)_nCH_2OH$ Where 'n' represents the average number of oxyethylene groups.
Physicochemical properties:	White or almost white solid with a waxy or paraffin-like appearance.
Solubility in water:	Very soluble in water and in methylene chloride, slightly soluble in alcohol, practically insoluble in fatty oils and in mineral oils.

2) Ascorbic Acid

Proper name:	Ascorbic Acid
Chemical name:	L-threo-hex-2-enioic acid y-lactone 3-oxo-L-gulofuranolactone (enol form)
Molecular formula and molecular mass:	$C_6H_80_6$ 176.13g/mol

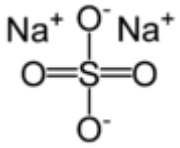
Structural formula:	
Physicochemical properties:	White or almost white, crystalline powder or colorless crystal, becoming discolored on exposure to air and moisture.
Solubility in water:	Freely soluble in water, soluble in ethanol (96 per cent)

3) Sodium Ascorbate

Proper name:	Sodium Ascorbate
Chemical name: Other names:	L-ascorbic acid monosodium salt E301 (Sodium Ascorbate)
Molecular formula and molecular mass:	$C_6H_7Na0_6$ 198.11
Structural formula:	
Physicochemical properties:	White to yellowish, crystalline powder or crystals.
Solubility in water:	Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

4) Sodium Sulphate Anhydrous

Proper name:	Sodium Sulphate Anhydrous
Chemical name: Other non-proprietary names:	Sodium sulphate anhydrous Sulphuric acid, Disodium salt, Disodium sulphate, Natrii sulfis anhydricus

Molecular formula and molecular mass:	Na_2SO_4 142.04
Structural formula:	
Physicochemical properties:	white or almost white powder
Solubility in water:	Freely soluble in water, very slightly soluble in ethanol (96 per cent).

5) Sodium Chloride

Proper name:	Sodium Chloride
Chemical name:	Sodium chloride, Natrii chloridum
Molecular formula and molecular mass:	NaCl 58.43
Structural formula:	NaCl
Empirical Formula:	NaCl
Physicochemical properties:	white or almost white, crystalline powder or colorless crystals or white or almost white pearls.
Solubility in water:	freely soluble in water, practically insoluble in anhydrous ethanol.

6) Potassium Chloride

Proper name:	Potassium Chloride
Chemical name:	Potassium Chloride
Molecular formula and molecular mass:	K^+Cl^- 74.55
Structural formula:	KCl

Empirical Formula:	KCl
Physicochemical properties:	white or almost white, crystalline powder or colorless crystals.
Solubility in water:	Freely soluble in water, practically insoluble in anhydrous ethanol

CLINICAL TRIALS

Study demographics and trial design

The colon cleansing efficacy and safety of MOVIPREP was evaluated in two multicentre, randomized, investigator-blinded, actively-controlled phase III trials, in patients scheduled to have an elective colonoscopy.

In the phase III clinical studies, MOVIPREP was administered in adults 18 years of age or older using either a single or a split dosing regimen.

The quality of bowel cleansing was assessed during colonoscopy by an experienced colonoscopist and/or independently reviewed by a blinded expert panel using videotapes recorded during the procedure.

Table 3 summarizes the patient demographics and basic trial design for the studies.

Table 3: Summary of Study Demographics and Trial Design for Phase III Clinical Trials

Study #	Trial design	Efficacy parameters	Dosage, route of administration and duration	Study subjects n=number	Mean age (Range)	Gender % M/F
NRL994-01/2001 Germany Phase III	Multicenter, randomized, parallel-group, investigator-blinded, active controlled	Overall colon cleansing Assessment by blinded expert panel	2L MOVIPREP Oral solution + 1L clear fluid Split-dose[1] <u>Versus</u> 4L PEG + E[2] Oral solution Split-dose[1]	153 155	58.0 (18-83) 59.6 (19-88)	51.6/48.4 45.8/54.2

NRL994-02/2001 France Phase III	Multicenter, randomized, parallel-group, investigator-blinded, active controlled	Overall colon cleansing Assessment by blinded expert panel and by colonoscopist	2L MOVIPREP Oral solution + 1L clear fluid Full-dose[3] Versus 90 mL OSPS[4] Oral solution + ≥2L clear fluid Full-dose[3]	137 143	52.4 (21-74) 52.4 (21-76)	55.3/46.7 52.4/47.6

[1] Split-dose: Split into two doses (during the evening before and the morning of the colonoscopy).
[2] 4L PEG + E: 4 litres of Polyethylene Glycol plus Electrolytes Solution.
[3] Full-dose: Only in the evening prior to the colonoscopy.
[4] OSPS: Oral Sodium Phosphate Solution.

Study results

Overall Colon Cleansing

Table 4 presents the results of the effectiveness of overall colon cleansing observed in the phase III clinical trials conducted with MOVIPREP.

Table 4: Effectiveness of Overall Colon Cleansing in the Phase III Clinical Trials Conducted with MOVIPREP

	Success Rate (Grade A[1] or B[2]) n (%)	**Grade C[3] n (%)**	**Grade D[4] n (%)**
Study NRL994-01/2001			
MOVIPREP (N=153)	136 (88.9)	15 (9.8)	2 (1.3)
4L PEG + E[5] (N=155)	147 (94.8)	7 (4.5)	1 (0.6)
Study NRL994-02/2001			
MOVIPREP (N=137)	100 (73.0)	32 (23.4)	5 (3.6)
90 mL OSPS[6] (N=143)	92 (64.4)	42 (29.4)	9 (6.3)

[1] A: Colon empty and clean or presence of clear liquid, but easily removed by suction.
[2] B: Brown liquid or semisolid remaining amounts of stool, fully removable by suction or displaceable, thus allowing a complete visualization of the gut mucosa.
[3] C: Semisolid amounts of stool, only partially removable with a risk of incomplete visualization of the gut mucosa.
[4] D: Semisolid or solid amounts of stool; consequently colonoscopy incomplete or needed to be terminated.
[5] 4L PEG + E: 4 Litre Polyethylene Glycol plus Electrolytes Solution.
[6] OSPS: Oral Sodium Phosphate Solution.

MOVIPREP responder rates were not significantly different than the comparator responder rates.

In the clinical trials, MOVIPREP was at least as effective as a bowel cleansing preparation for colonoscopy as the comparator products tested.

Patient acceptability

The pooled data demonstrate that the patients in the MOVIPREP arms of these studies found the dietary restrictions more satisfactory than those in the comparator arms. In total, 266 patients (91.7%) who received MOVIPREP rated the acceptability of the diet as very or fairly satisfactory, compared with 206 patients (69.1%) who received comparator products. In addition, 199 patients (68.6%) found the taste of MOVIPREP acceptable or satisfactory, compared with 154 patients (51.7%) who found the taste of the comparator acceptable or satisfactory. For both MOVIPREP and the comparator agents, the majority of patients consumed the entire volume of solution with no problem.

These results demonstrate that MOVIPREP is at least as acceptable to the patient as the comparator products tested.

DETAILED PHARMACOLOGY

No in vivo pharmacology studies were conducted with MOVIPREP.

The three principle active ingredients in MOVIPREP (macrogol 3350, sodium sulphate, ascorbic acid/sodium ascorbate) act synergistically to produce a greater increase in osmolality than would be predicted from the sum of their individual molar concentrations. This is due, primarily, to the sequestration of water by macrogol (polyethylene glycol, PEG). The result is that a fraction of the water is prevented from interacting with the products of dissociation, thus increasing their concentration in the volume of water available. Due to the increased concentration of sodium ions, faecal water volume increases beyond that which would be predicted from the volume and osmolality of the ingested MOVIPREP. Increased water consumption may be observed.

Pharmacodynamics

The desired clinical effect of expanding faecal volume is produced primarily as a factor of their physical chemistry, the result of which is to increase the osmotic flow of water into the colon.

- Macrogol (Polyethylene Glycol): Macrogol (PEG) acts by sequestering water.
- Sodium Sulphate: Sodium sulphate is present primarily as an osmotic agent.
- Ascorbic Acid/Sodium Ascorbate: The physiological need for ascorbic acid has been well studied. In humans and some animals, an exogenous source of ascorbic acid

(Vitamin C) is required for collagen formation and tissue repair. It is also needed in oxidation-reduction reactions, tyrosine metabolism, synthesis of lipids and proteins, and the metabolism of folic acid, iron and carbohydrates. Ascorbic acid is also involved in cellular respiration and assists with resistance to infections. The main action of ascorbic acid in MOVIPREP, however, is to increase osmotic flow of water into the colon.

A series of laboratory investigations demonstrated the synergistic effects of the three osmotic agents.

- Osmolality was determined for each ingredient in MOVIPREP. Results were consistent with the theory that interactions between high concentrations of macrogol (PEG) and water molecules alter their physical properties and, as a result, sequester water from the solution. Less water is available to interact with the sodium and sulphate ions, and ascorbic acid, thereby increasing the osmotic activity of the solute to levels higher than theoretical values.
- Osmolality was determined for macrogol (PEG) 3350 alone or in combination with sodium sulphate, sodium sulphate and sodium chloride, or with sodium sulphate, sodium chloride and potassium chloride in solution at the levels contained in the MOVIPREP formulation. The cumulative effect macrogol (PEG) 3350 had on the osmolality of other dissociable ingredients in Pouch A was again greater than calculated values (Table 5).

Table 5: Comparison of Measured vs. Calculated Osmolality

Ingredients in Solution (at MOVIPREP levels)	**Measured Osmolality (average mOsm/kg)**	**Calculated Theoretical Osmolality (mOsm/kg)**
Macrogol (PEG) 3350	115	29.9
PEG 3350 and Na_2SO_4	316	188.3
PEG 3350, Na_2SO_4 and NaCl	416	280.4
PEG 3350, Na_2SO_4, NaC1 and KCl	446	307.6

- Osmolality and associated water binding was further investigated by utilising varying concentrations of macrogol (PEG) 3350 combined with anhydrous sodium sulphate independently, sodium ascorbate independently, or sodium ascorbate combined with ascorbic acid. Only macrogol (PEG) 3350 varied in concentration; all other components were maintained at formulation levels. Various parameters were calculated including the volume of water “bound”. The results from this study demonstrated that the volume of water bound increased as the concentration of macrogol (PEG) 3350 increased. These results were consistent with the previous two studies, i.e. that macrogol (PEG) sequesters water from solution, and, therefore, macrogol (PEG) can affect the chemical and osmotic activity of sodium ions in solution.

- The volume of deionised water required to provide a measured osmolality of 350 mOsm/kg (taken as the osmolality of faecal water) for MOVIPREP in solution was also investigated. It was determined that 0.43 mL of additional water is required to bring a 1.0 mL MOVIPREP solution, (14.0 mL MOVIPREP brought to 20 mL volume), to a measured osmolality of 350 mOsm/kg + 2% mOsm/kg. These results indicate that for the recommended dosage of MOVIPREP (Pouch A+B in 1L of water, taken twice), the 2L volume consumed would expand to 2.86L when diluted to the osmolality of faecal water.

Safety Pharmacology
No safety pharmacology studies were conducted with MOVIPREP.

The main safety issue related to the use of MOVIPREP, particularly in vulnerable patients, is a potential shift of electrolytes between body compartments at extremely high doses of osmotically active agents in the gut. This is addressed by adding a balance of electrolytes and controlling the flow of water across the wall of the colon.

Pharmacodynamic Drug Interactions
No pharmacodynamic drug interaction studies were performed with MOVIPREP.

The literature does indicate that large doses of ascorbic acid (1g vitamin C daily), does increase the plasma concentration of ethinyloestradiol in women taking combined oral contraceptives, and this is followed by heavy breakthrough vaginal bleeding when vitamin C is stopped. It is not known whether this has an effect on contraceptive efficacy (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**).

Pharmacokinetics

No pharmacokinetic studies were conducted with MOVIPREP.

Absorption of macrogol (PEG) is dependant on its molecular weight. As the molecular weight increases, absorption is decreased so that at a molecular weight of 1300 and above only a very small percentage is absorbed. At the molecular weight of macrogol (PEG) in MOVIPREP (~3350), absorption would be expected to be negligible. The low percentage of macrogol (PEG) that is absorbed is predominantly likely to be excreted unchanged in the urine (with perhaps a small amount in the bile).

Some absorption of the other constituents of MOVIPREP may occur, although the process is likely to be self-limiting due to the saturability of their absorption and excretion mechanisms. Gut absorption of sodium sulphate is governed by a saturable absorption mechanism, with absorbed sodium and sulphate ions entering the cell pool and/or excreted in the urine. Similarly, absorption of ascorbic acid appears to be saturable; absorbed material is metabolised with a major metabolite being oxalate, but as the blood concentration increases, the amount of unmetabolised ascorbic acid increases in the urine. Therefore, sodium sulphate and ascorbic acid are both absorbed well, but the majority of the high concentrations in MOVIPREP remain in the gut due to limitations on absorption

and excretion saturation mechanisms. Excess sodium chloride and potassium chloride are well absorbed from the gut with use in the cell pool or urinary excretion. At the proposed level of use, systemic exposure to aspartame or its metabolites will likely not occur and any absorbed acesulfame potassium will be likely quickly cleared.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

MOVIPREP contains macrogol (polyethylene glycol) 3350, sodium sulphate anhydrous, sodium chloride, potassium chloride, aspartame, acesulfame potassium, lemon flavor V3938-1N1, ascorbic acid, and sodium ascorbate. The toxicology of the individual ingredients is relatively well characterized in the literature.

Single-Dose Toxicity
No single-dose toxicity studies were conducted with MOVIPREP.

In a single-dose acute toxicity study in CD rats, Spray-Dried Lemon Flavouring V3938-1N1 (in tap water), the flavouring preparation used in MOVIPREP, was administered orally by gavage at 2000 mg/kg (5 rats/sex). No mortality, no clinical signs and no body weight changes were noted for up to 14 days following administration. The LD_{50} was estimated to be greater than 2000 mg/kg at both 24 hours and 14 days in males and females.

In a preliminary study, single dosages of 50 to 5000 mg/kg Spray-Dried Lemon Flavouring V3938-1N1 were administered and slight to moderate signs of toxicity were noted within the first 24 hours at 3000 to 5000 mg/kg. At 3000 mg/kg, slightly reduced motility was observed. At 4000 and 5000 mg/kg, slight dyspnea and moderately reduced motility were noted.

Repeat-Dose Toxicity

Table 6: Summary of Principal Findings in Repeat-Dose Toxicity Studies Conducted with MOVIPREP

Species and Strain	Method of Administration	Duration of Dosing	Doses (g/kg/day)	Gender & No. per Group	Noteworthy Findings
Rat CD	Oral Gavage	14 days + 4-week recovery period	Control (Tap water) MOVIPREP: -5 g/kg/day -10 g/kg/day -20 g/kg/day	Main study: 10M + 10F /group (4 groups) Recovery: 5M + 5F /group (control and high dose groups) TK: 9M + 9F /group (3 test groups) 3M + 3F (control)	Two animals (1M + 1F) treated with 20 g/kg/day MOVIPREP died. Deaths were considered treatment-related but the cause for the deaths was not known. Signs of systemic effects in the form of soft faeces, increased water consumption, reduced food consumption, changes in biochemical and urinary parameters (increased bilirubin, ALAT and urea, decreased chloride and potassium levels, and increased urine specific gravity), and increased absolute and relative kidney weights were noted at 20 g/kg/day. Systemic effects were also noted at 10 g/kg/day with reduced food consumption and changes in biochemical and urinary parameters (increased urea and decreased chloride and potassium levels, and increased urine specific gravity). Changes observed appeared to have subsided at the end of the 4-week recovery period. TK: Plasma samples for ascorbic acid, employing ascorbic acid as an indicator for systemic exposure (as macrogol [PEG] 3350 is essentially not absorbed), revealed a dose-related systemic exposure (ranged from 5.0 to 40.9 ug/mL). No apparent signs of accumulation of the ascorbic acid were noted. Higher values were noted for C_{max}- and $AUC_{0\text{-}8\,h}$-values in males compared to females.
Dog Beagle	Oral Gavage	14 days + 2-week recovery period	Control (Tap water) MOVIPREP: -5 g/kg/day -10 g/kg/day -20 g/kg/day	Main Study: 3M + 3F /group (4 groups) Recovery: 2M + 2F /group (control and high dose groups)	Signs of systemic response in the form of defecation, emesis and pultaceous to liquid (diarrhoea) faeces were noted in all treatment groups. Salivation and a decreased sodium level were also noted in the high dose group. The severity and incidence of the findings increased with the dose level. Changes observed appeared to have subsided at the end of the 2-week recovery period. TK: Plasma samples for ascorbic acid, employing ascorbic acid as an indicator for systemic exposure (as macrogol [PEG] 3350 is essentially not absorbed), revealed a dose-related systemic exposure (ranged from 5.0 to 55.0 ug/mL). No apparent signs of accumulation of the ascorbic acid were noted. Higher values were noted for C_{max}- and $AUC_{0\text{-}8\,h}$-values in females compared to males.

ALAT: alanine aminotransferase; F: Female; M: Male; PEG: Polyethylene Glycol; TK: Toxicokinetics.

In summary, the toxicity profiles of MOVIPREP were characterized in 2-week oral toxicity studies in rats and dogs. Overall, the results indicated that the kidney appeared to be the target organ of toxicity in rats based on the changes of the clinical chemistry and kidney weight. In dogs, the results suggested that the gastrointestinal tract appeared to be the target organ of toxicity based on the clinical signs of toxicity including emesis, diarrhea, and salivation.

Genotoxicity
No genotoxicity studies were conducted with MOVIPREP.

In a mutagenicity study, Lemon Flavoring V3938-1N1 (the flavouring preparation used in MOVIPREP) showed no evidence of mutagenic effect in the *Salmonella tyhimurium* strains and the *Escherichia coli* strain when tested up to the cytotoxic concentration of 5000 µg/plate in the plate incorporation test or up to 3160 µg/plate in the pre-incubation test, either in the presence or absence of metabolic activation.

There is evidence from the literature that demonstrates that ascorbate may have mutagenic potential. Ascorbate induced a dose-dependent increase in sister-chromatid exchanges (SCE) in Chinese hamster ovary (CHO) cells and in human lymphocytes, as well as increased the inhibition of DNA synthesis in Hela cells. Ascorbate also induced mutation at the hypoxanthineguanine phosphoribosyl transferase (HGPRT) locus in CHO cells.

Carcinogenicity
No carcinogenicity studies were conducted with MOVIPREP.

Reproductive and Developmental Toxicity
No reproductive and developmental toxicity studies and no studies in juvenile animals were conducted with MOVIPREP.

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PART III: CONSUMER INFORMATION

MOVIPREP®

Macrogol (PEG) 3350, Sodium sulphate anhydrous, Sodium chloride, Potassium chloride, Ascorbic acid, Sodium ascorbate

This leaflet is part III of a three-part "Product Monograph" published when MOVIPREP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MOVIPREP. Contact your doctor or pharmacist if you have any questions about the drug.

MOVIPREP can only be recommended by your doctor.

ABOUT THIS MEDICATION

What the medication is used for:
MOVIPREP helps empty the bowel (colon) as a preparation for colonoscopy in adults 18 years of age and older.

What it does:

All the ingredients in MOVIPREP act together to increase stool volume by attracting water to the stool, which stimulates the bowel to expel the contents in a laxative effect. The removal of bowel contents makes the clinical examination and visualization of the tissue easier.

What you should expect to happen:

When you start drinking the MOVIPREP solution, it is important that you stay close to a toilet. At some point, you will start to experience watery bowel movements. This is quite normal and indicates that the MOVIPREP solution is working. The bowel movements will stop soon after you have finished drinking.

If you follow these instructions, your bowel will be clear, and this will help you to have a successful examination.

When it should not be used:
DO not take MOVIPREP if you suspect or your doctor suspects**:**

- You have serious conditions of the abdomen such as appendicitis or diverticulitis (fold within the intestinal wall which may be swollen and infected);
- You are allergic (hypersensitive) to Macrogol 3350 (Polyethylene glycol 3350) or any of the other ingredients of MOVIPREP (see what the non-medicinal ingredients are).
- You have an obstruction in your intestine (gut).
- You have a perforated gut wall.
- You have a disorder of stomach emptying.
- You have paralysis of the gut (often occurs after an operation to the abdomen).
- you have toxic megacolon (a severe complication of acute colitis).

What the medicinal ingredient is:
Sachet A contains the following medicinal ingredients:

Macrogol (also known as polyethylene glycol) 3350	100 g
Sodium sulphate anhydrous	7.5 g
Sodium chloride	2.691 g
Potassium chloride	1.015 g

Sachet B contains the following medicinal ingredients:

Ascorbic acid	4.7 g
Sodium ascorbate	5.9 g

What the important nonmedicinal ingredients are:
MOVIPREP powder for oral solution, contains the following nonmedicinal ingredients: acesulfame potassium (E950) and aspartame (E951) as sweeteners, lemon flavouring (containing citral, lemon oil, lime oil, maltodextrin, vitamin E, xanthan gum,).

What dosage forms it comes in:
MOVIPREP is a lemon flavoured powder for oral solution contained in four sachets. There are two large sachets ('Sachet A') and two small sachets ('Sachet B'). You need all these for one treatment.

The concentration of electrolyte ions when both sachets are made up to one litre of solution is as follows:

Sodium	181.6 mmol/l (of which not more than 56.2 mmol is absorbable)
Sulphate	52.8 mmol/l
Chloride	59.8 mmol/l
Potassium	14.2 mmol/l
Ascorbate	29.8 mmol/l

The osmolarity of the final reconstituted solution is 560 mOsmol.

WARNINGS AND PRECAUTIONS

If you are in poor health or have a serious medical condition, you should be particularly aware of the possible side effects listed in section "Side Effects and What to Do About Them". Contact your doctor or pharmacist if you are concerned.

Before you use MOVIPREP, talk to your doctor or pharmacist if you have:
- kidney disease.
- heart failure.
- dehydration.
- acute flare of inflammatory bowel disease (Crohn's disease or ulcerative colitis).
- phenylketonuria, (PKU - an inability to use the amino acid phenylalanine) - this product contains phenylalanine which can harm individuals with PKU.
- not enough glucose-6-phosphate dehydrogenase produced by your body.
- a history of electrolyte imbalance (e.g. hyponatremia).

- In rare cases, serious heart arrhythmias (an irregular or fast heartbeat) have been associated with the use of medicines such

as MOVIPREP. Tell your doctor if you have problems with your heart such as:
- a history of an abnormal electrical signal called "prolongation of the QT interval"
- an arrhythmia that is not under control
- a recent heart attack
- heart failure
- cardiomyopathy (a disease of the heart muscle that makes it harder for your heart to pump blood to the rest of your body)

Your doctor will decide whether you can take MOVIPREP.

Talk to your doctor about all the medications you are taking or planning to take (see Interactions with this medication)

Talk to your doctor if you have any tendency to regurgitate (bring up) food from your stomach into your esophagus or any tendency to accidentally inhale food or regurgitate food into the airways (breathing tube to the lung).

Talk to your doctor if you need to thicken fluids in order to swallow them safely. MOVIPREP contains polyethylene glycol (PEG), which may stop starch based food thickeners from working. This may cause certain mixtures to be watery and difficult to swallow.

MOVIPREP should not be given to patients with impaired consciousness without medical supervision.

Contact your doctor immediately and stop taking the drug if the following occurs while taking MOVIPREP:
- abdominal pain, bloating, swelling of the abdomen

Important information about some of the ingredients of MOVIPREP
This medicinal product contains 56.2 mmol of absorbable sodium per litre. To be taken into consideration by patients on a controlled sodium diet.
This medicinal product contains 14.2 mmol of potassium per litre. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

This medicinal product contains a source of phenylalanine which may be harmful for people with phenylketonuria.

Pregnancy and breastfeeding
There are no data on the use of MOVIPREP during pregnancy or lactation and it should only be used if considered essential by the physician. So if you are pregnant or breastfeeding talk to your doctor before taking MOVIPREP.

INTERACTIONS WITH THIS MEDICATION

Drug interaction studies have not been performed for MOVIPREP.
Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including diuretics and angiotensin converting enzyme inhibitor (ACE inhibitors- heart medication) and medicines obtained without a prescription.

Taking MOVIPREP with food and drink
Do not take any solid food from when you start to take MOVIPREP until after the examination.

PROPER USE OF THIS MEDICATION

Usual dose: Adults 18 years of age and older:
Always take MOVIPREP exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is 2 litres of solution, which is made up as follows:

This pack contains 2 clear bags each containing one pair of sachets: Sachet A and Sachet B. Each pair of sachets (A and B) is to be dissolved in water to make a one litre solution. This pack is therefore sufficient to make up 2 litres of MOVIPREP solution.

You should have been given instructions about when to take MOVIPREP by your doctor or nurse. Your treatment with MOVIPREP must be completed before your clinical examination.

How to drink MOVIPREP

This product can be taken as either as single dose or in 2 doses as per following:

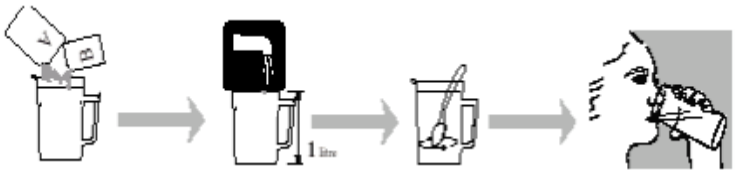
Single dose:
Take the entire dose of 2 litres in the evening before the examination in the following steps:
a) Drink the first litre of the Moviprep solution over one or two hours. Try to drink a glassful every 10-15 minutes.
b) When you are ready, make up the second 1 litre solution and drink the same way, the evening before the examination.
c) During the course of treatment, you are recommended to drink a further litre of clear liquid to prevent you from feeling thirsty and becoming dehydrated. Water, clear soup, fruit juice (without pulp, soft drink, tea or coffee (without milk) are all suitable. These drinks can be taken any time.

Divided Dose:
a) Drink the first litre of the MOVIPREP solution over one or two hours the evening before the examination. Try to drink a glassful every 10-15 minutes.
b) The next morning, make up and drink the second 1 litre solution and drink the same way.
c) During the course of treatment, you are recommended to drink a further litre of clear liquid to prevent you from feeling thirsty and becoming dehydrated. Water, clear soup, fruit juice (without pulp), soft drink, tea or coffee (without milk) are all suitable. These drinks can be taken any time.

Important: Do not take any solid food from when you start to take MOVIPREP until after the examination.

How to prepare MOVIPREP

- Open one clear bag and remove the sachets A and B.
- Add the contents of BOTH sachet A and sachet B to a 1 litre container.
- Pour 1 litre of water into the container and stir until all the powder has dissolved and the MOVIPREP solution is clear or slightly hazy. This may take up to 5 minutes.



Overdose:

If you think you have taken too much MOVIPREP, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

If you take more MOVIPREP than you should you may develop excessive diarrhoea, which can lead to dehydration. Take generous amounts of fluid, especially fruit juices.

Missed Dose:
If you forget to take MOVIPREP take the dose as soon as you realize you have not taken it. If this is several hours after the time when you should have taken it, contact your doctor or pharmacist for advice. It is important that you complete your preparation at least an hour before your procedure.

If you do not have a bowel movement within 6 hours of taking MOVIPREP, stop the intake and contact your doctor immediately.

If you are taking other medicines take them at least one hour before or after taking MOVIPREP, otherwise they may flush through your system and will not work so well.

If you have any further questions on the use of this product, ask your doctor or pharmacist

Children

MOVIPREP should not be taken by children aged below 18 years.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, MOVIPREP can have side effects although not everybody gets them.

It is normal to get diarrhoea when you take MOVIPREP.

Very common side effects (i.e. occurring in more than 1 in 10 patients who received the treatment) are: Abdominal pain, abdominal distension, tiredness, feeling generally unwell, soreness of the anus, and nausea.

Common side effects (i.e. occurring in less than 1 in 10 but more than 1 in 100 patients who received the treatment) are: Hunger, problems sleeping, dizziness, headache, vomiting, indigestion, upper abdominal pain, thirst and chills.

Uncommon side effects (i.e. occurring in less than 1 in 100 but more than 1 in 1,000 patients who received the treatment): Change to the levels of salts in the blood.

Blood sodium levels could also decrease particularly in patients taking medicines that affect the kidney such as ACE Inhibitors and diuretics used for the treatment of heart disease.

Very low blood sodium levels can cause convulsions (fits).

Use of PEG-based products (polyethylene glycol) have resulted in seizures.

Other side effects that may occur include flatulence (wind), temporary increase in blood pressure, and some people may experience retching (straining to vomit).

These reactions usually only occur for the duration of the treatment. Should they persist, consult your doctor.

Allergic reactions may occur.

If you experience any of the following, stop taking MOVIPREP and contact your doctor immediately as these may the signs of an allergic reaction or an electrolytes imbalance in the blood:

- rash or itching
- swelling of your face, ankles, throat, mouth or extremities
- palpitations (rapid heartbeat)
- extreme fatigue
- shortness of breath, difficulty in breathing

If any of the side effects become serious, or if you notice any of the side effects not listed in this leaflet, please tell your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect		**Talk with your doctor or pharmacist**	**Stop taking drug and call your doctor or pharmacist**
Common	Upper abdominal pain	**X**	
Uncommon	**Electrolyte imbalance** in the blood with symptoms such		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect		**Talk with your doctor or pharmacist**	**Stop taking drug and call your doctor or pharmacist**
	as palpitations, extreme fatigue, swelling of tissues, weakness **Hypersensivity (allergic)** reaction with symptoms such as: rash, itching, hives, swelling of tissues, difficulty breathing	**X**	

If the following symptoms as hunger, problems sleeping, dizziness, headache, indigestion, thirst and chills become bothersome or persist, contact your doctor.

This is not a complete list of side effects. For any unexpected effects while taking MOVIPREP, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach of children.

Do not use MOVIPREP after the expiry date which is stated on the carton and sachets.
The expiry date refers to the last day of the month.

Keep MOVIPREP sachets at temperature between 5°C -25°C.

After you have dissolved MOVIPREP in the water, the solution may be stored (keeping covered) at temperature 15°C -25°C. It may also be stored in the fridge (2ºC -8ºC). Discard solution 24 hours after reconstitution.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Remember: Only a doctor can prescribe it for you. Never give it to someone else.

This leaflet does not contain the complete information about your medicine. If any questions remain unanswered or you are not sure about something, you should ask your doctor or pharmacist.

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.aralez.com or by contacting the sponsor,
Aralez Pharmaceuticals Canada Inc.
Mississauga, ON at:
1-866-391-4503

This leaflet was prepared by Aralez

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