

# Public Assessment Report

**Moviprep**

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

**UK/H/891/01/MR**

**Norgine B.V.**

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## Module 1

<b>Product Name</b>	Moviprep
<b>Type of Application</b>	Mutual Recognition Procedure
<b>Active Substance</b>	Macrogol 3350 Sodium sulphate, anhydrous Sodium chloride Potassium chloride Ascorbic acid Sodium ascorbate
<b>Form</b>	Oral powder for solution
<b>Strength</b>	Not applicable
<b>MA Holder</b>	Norgine BV Hogehilweg 7, 1101CA Amsterdam ZO The Netherlands
<b>Nba1968mj</b>	UK
<b>CMS</b>	Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, The Netherlands, Spain and Sweden
<b>Procedure Number</b>	UK/H/891/01
<b>MA Number</b>	PL 20142/0005 Formerly PL 00322/0084
<b>Timetable</b>	Granted 19 <sup>th</sup> January 2006

## Module 2

### MOVIPREP SUMMARY OF PRODUCT CHARACTERISTICS

#### name of the medicinal product

MOVIPREP sachets, powder for oral solution

#### Qualitative and Quantitative Composition

The ingredients of MOVIPREP are contained in two separate sachets.

**Sachet A** contains the following active substances:

Macrogol 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

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

This product contains 0.233 g of aspartame per sachet A.

For a full list of excipients, see section 6.1.

#### Pharmaceutical Form

Powder for oral solution.

Free flowing white to yellow powder in Sachet A.

Free flowing white to light brown powder in Sachet B.

#### Clinical Particulars

#### 4.1 Therapeutic indications

For bowel cleansing prior to any clinical procedures requiring a clean bowel e.g. bowel endoscopy or radiology.

#### 4.2 Posology and method of administration

**Adults and elderly:** 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:

- either divided as one litre of MOVIPREP in the evening before and one litre of MOVIPREP in the early morning of the day of the clinical procedure,
- or, in the evening preceding the clinical procedure.

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.

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

#### 4.3 Contra-indications

Do not use in patients with known or suspected:

- gastrointestinal obstruction or perforation
- disorders of gastric emptying (e.g. gastroparesis)
- ileus
- phenylketonuria (due to presence of aspartame)
- glucose-6-phosphate dehydrogenase deficiency (due to presence of ascorbate)
- hypersensitivity to any of the ingredients
- toxic megacolon which complicates severe inflammatory conditions of the intestinal tract including Crohn's disease and ulcerative colitis.

Do not use in unconscious patients.

#### 4.4 Special warnings and precautions for use

Diarrhoea is an expected effect resulting from the use of MOVIPREP.

MOVIPREP should be administered with caution to fragile patients in poor health or patients with serious clinical impairment such as:

- impaired gag reflex, or with a tendency to aspiration or regurgitation
- impaired consciousness
- severe renal insufficiency (creatinine clearance <30 ml/min)
- cardiac impairment (NYHA grade III or IV)

- dehydration
- severe acute inflammatory disease

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

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

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.

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.

If patients experience symptoms such as severe bloating, abdominal distention, abdominal pain or any other reaction which makes it difficult to continue the preparation, they may slow down or temporarily stop consuming MOVIPREP and should consult their doctor.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

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 therapeutic effect of drugs with a narrow therapeutic index or short half-life may be particularly affected.

#### **4.6 Pregnancy and lactation**

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.

#### **4.7 Effects on ability to drive and use machines**

There is no known effect on the ability to drive and use machines.

#### **4.8 Undesirable effects**

The frequency of adverse reactions to MOVIPREP is defined using the following convention:

Very common  $\geq 1/10$  ( $\geq 10\%$ );

Common  $\geq 1/100$ ,  $< 1/10$  ( $\geq 1\%$   $< 10\%$ );

Uncommon  $\geq 1/1,000$ ,  $< 1/100$  ( $\geq 0.1\%$   $< 1\%$ );

Rare  $\geq 1/10,000$ ,  $< 1/1,000$  ( $\geq 0.01\%$   $< 0.1\%$ );

Very rare  $< 1/10,000$  ( $< 0.01\%$ ).

Diarrhoea is an expected outcome of bowel preparation. Due to the nature of the intervention, undesirable effects occur in the majority of patients during the process of bowel preparation. Whilst these vary between preparations, nausea, vomiting, bloating, abdominal pain, anal irritation and sleep disturbance commonly occur in patients undergoing bowel preparation.

As with other macrogol containing products, allergic reactions including rash, urticaria, oedema and anaphylaxis are a possibility.

Data from clinical studies are available in a population of 591 patients treated with MOVIPREP in which undesirable effect data were actively elicited.

Body System	Adverse drug reaction
<b>Metabolism and nutrition disorders</b>	
Common:	hunger
Uncommon	hypophosphatemia
<b>Psychiatric disorders</b>	
Common	sleep disorder
<b>Nervous system disorders</b>	
Common	dizziness
Uncommon	headache
<b>Gastrointestinal disorders</b>	
Very common	abdominal pain , nausea , abdominal distension, anal discomfort ,
Common	vomiting, dyspepsia
Uncommon	dysphagia
<b>General disorders and administration site conditions</b>	
Very common	
Common	malaise, thirst
Uncommon	rigors
<b>Investigations</b>	discomfort
Uncommon	blood bicarbonate decreased:, blood calcium decreased:, hypercalcaemia:, blood chloride decreased:, blood chloride increased:, blood phosphorus decreased:, liver function tests abnormal

#### 4.9 Overdose

In case of gross accidental overdosage, where diarrhoea is severe, conservative measures are usually sufficient; generous amounts of fluid, especially fruit juices, should be given. In the rare event of overdose provoking severe metabolic derangement, intravenous rehydration may be used.

### Pharmacological Properties

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A06A D

Macrogol 3350, sodium sulphate and high doses of ascorbic acid exert an osmotic action in the gut, which induce a laxative effect. The electrolytes present in the formulation as well as the supplementary clear liquid intake ensure that there are no clinically significant variations of sodium, potassium or water, and thus no dehydration risk.

#### 5.2 Pharmacokinetic properties

Macrogol 3350 is unchanged along the gut. It is virtually unabsorbed from the gastrointestinal tract and has no known pharmacological activity. Any macrogol 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.

### **5.3 Pre-clinical safety data**

Pre-clinical studies provide evidence that macrogol 3350, ascorbic acid and sodium sulphate have no significant systemic toxicity potential.

## **Pharmaceutical Particulars**

### **6.1 List of excipients**

Aspartame (E951)

Acesulfame Potassium (E950)

Lemon flavour containing maltodextrin, citral, lemon oil, lime oil, xanthan gum, vitamin E.

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

Sachets	3 years
Reconstituted solution	24 hours

### **6.4 Special precautions for storage**

Sachets: Store below 25°C. Store in the original package.

Reconstituted Solution: Store below 25°C. The solution may be refrigerated. Keep the solution covered.

### **6.5 Nature and contents of container**

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

### **6.6 Special precautions for disposal and other handling**

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.

## **MARKETING AUTHORISATION HOLDER**

Norgine BV  
Hogehilweg 7, 1101CA  
Amsterdam ZO  
The Netherlands



**MARKETING AUTHORISATION NUMBER(S)**

**DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

19/01/2006

**DATE OF REVISION OF THE TEXT**

02/10/2006

## Module 3

### Package LEAFLET: INFORMATION FOR THE USER

**MOVIPREP<sup>®</sup>** powder for oral solution in sachets  
For a list of active substances please see section 6.

**Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**

1. What MOVIPREP is and what it is used for
2. Before you take MOVIPREP
3. How to take MOVIPREP
4. Possible side effects
5. How to store MOVIPREP
6. Further information

### 1. WHAT MOVIPREP IS AND WHAT IS IT USED FOR

MOVIPREP is a lemon flavoured powder contained in four sachets. There are two large sachets ('Sachet A') and two small sachets ('Sachet B'). You need all these for one treatment.

You are taking MOVIPREP to make your bowels clean so that they are ready for examination. MOVIPREP works by emptying the contents of your bowels, so you should expect to have watery bowel movements.

### 2. BEFORE YOU TAKE MOVIPREP

**Do not take MOVIPREP** if you suspect or your doctor suspects:

- you are allergic (hypersensitive) to macrogol 3350 or any of the other ingredients of MOVIPREP.
- 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 suffer from phenylketonuria. This is an hereditary inability of the body to use a particular amino acid. MOVIPREP contains a source of phenylalanine.
- your body is unable to produce enough glucose-6-phosphate dehydrogenase.
- you have toxic megacolon (a severe complication of acute colitis).

**Take special care with MOVIPREP**

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 4. Contact your doctor or pharmacist if you are concerned.

You should tell your doctor before taking MOVIPREP if you have any of the following:

- you need to thicken fluids in order to swallow them safely.
- a tendency to regurgitate swallowed drink, food or acid from the stomach.
- kidney disease.
- heart failure.
- dehydration.
- acute flare of inflammatory bowel disease (Crohn's disease or ulcerative colitis).

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

**Taking other medicines**

If you are taking other medicines take them at least one hour before taking MOVIPREP or at least one hour afterwards because they may be flushed through your digestive system and not work so well.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including 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.

**Pregnancy and breast-feeding**

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.

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**

MOVIPREP does not affect your ability to drive or use machines.

**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.

Contains a source of phenylalanine. May be harmful for people with phenylketonuria.

**3. HOW TO TAKE MOVIPREP**

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 two pairs of sachets: Sachet A and Sachet B. Each pair of sachets (A and B) is to be dissolved in one litre of water. This pack is therefore sufficient to make up 2 litres of MOVIPREP solution.

Before you take MOVIPREP, please read carefully the following instructions. You need to

know:

- When to take MOVIPREP
- How to prepare MOVIPREP
- How to drink MOVIPREP
- What you should expect to happen

### When to take MOVIPREP

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 and can be taken:

*either*

divided as 1 litre of MOVIPREP in the evening before and 1 litre in the early morning of the day of the examination,

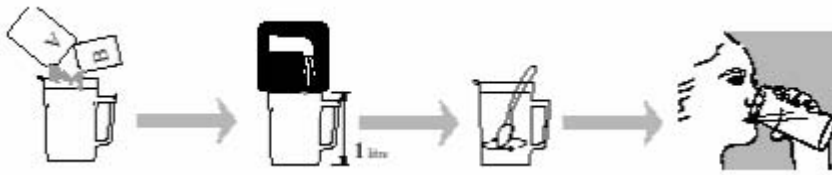
*or*

2 litres in the evening before the examination,

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.



### How to drink MOVIPREP

Drink the first litre of the MOVIPREP solution over one to two hours. Try to drink a glassful every 10-15 minutes.

When you are ready, make up and drink the second litre of MOVIPREP solution made up with the contents of the sachets A and B from the remaining bag.

During the course of this treatment, you are recommended to drink a further one litre of *clear* liquid to prevent you feeling very thirsty and becoming dehydrated. Water, clear soup, fruit juice (*without pulp*), soft drinks, tea or coffee (*without milk*) are all suitable. These drinks can be taken at any time you choose.

### 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.

#### **If you take more MOVIPREP than you should**

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. If you are worried contact your doctor or pharmacist.

#### **If you forget to take MOVIPREP**

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 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.**

### **4. POSSIBLE SIDE EFFECTS**

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, soreness of the anus, thirst, 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, vomiting, indigestion 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) are: Headache, discomfort, difficulties swallowing, change to the levels of salts in the blood: decreased bicarbonate, increased or decreased calcium; increased or decreased chloride; decreased phosphorus and changes to tests of liver function.

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 your intake of MOVIPREP and contact your doctor immediately. You should not take any more MOVIPREP until you have checked with your doctor.

- rash or itching
- swelling of your face, ankles or other part of your body
- palpitations
- extreme fatigue
- shortness of breath

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

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.

## 5. STORING MOVIPREP

Keep out of the reach and sight 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 room temperature (not above 25°C).

After you have dissolved MOVIPREP in the water, the solution may be stored (keeping covered) at room temperature (not above 25°C). It may also be stored in the fridge (2°C -8°C). Do not keep it for more than 24 hours.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

## 6. FURTHER INFORMATION

**Sachet A** contains these active substances:

Macrogol (also known as polyethylene glycol) 3350	100 g
Sodium sulphate anhydrous	7.500 g
Sodium chloride	2.691 g
Potassium chloride	1.015 g

**Sachet B** contains these active substances:

Ascorbic acid	4.700 g
Sodium ascorbate	5.900 g

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

Other ingredients are:

Lemon flavouring (containing maltodextrin, citral, lemon oil, lime oil, xanthan gum, vitamin E), aspartame (E951) and acesulfame potassium (E950) as sweeteners.

### What MOVIPREP looks like and contents of the pack

This pack contains 2 clear bags each containing two pairs of sachets: Sachet A and Sachet B. Each pair of sachets (A and B) is to be dissolved in one litre of water.

### Marketing Authorisation Holder and Manufacturer

**Marketing Authorisation Holder:**

Norgine BV, Hogehilweg 7, 1101CA Amsterdam ZO, The Netherlands

**Manufacturer:**

Norgine Limited, New Road, Hengoed, Mid Glamorgan, CF82 8SJ, United Kingdom.

**The medicinal product is authorised in the Member States of the EEA under the following names:**

<u>Country</u>	<u>Tradename</u>	<u>MA Number</u>
United Kingdom	MOVIPREP	PL 00322/0084

**This leaflet was last approved in October 2006.**

The following information is intended for medical or healthcare professionals only.

Note for medical staff:

MOVIPREP should be administered with caution to fragile patients in poor health or patients with serious clinical impairment such as:

- impaired gag reflex, or with a tendency to aspiration or regurgitation
- impaired consciousness
- severe renal insufficiency (creatinine clearance <30 ml/min)
- cardiac impairment (NYHA grade III or IV)
- dehydration
- severe acute inflammatory disease

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

Semi-conscious patients or patients prone to aspiration or regurgitation should be closely observed during administration especially if this is via a nasogastric route.

## Module 4

### Labelling

#### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL ON CARTONS (Single treatment of four sachets)  
Contains one treatment of two sachets A and two sachets B.

#### 1. NAME OF THE MEDICINAL PRODUCT

MOVIPREP  
Powder for oral solution in sachets.

#### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

##### Sachet A

Each sachet A contains:

Macrogol 3350	100 g
Sodium sulphate	7.500 g
Sodium chloride	2.691 g
Potassium chloride	1.015 g

##### Sachet B

Each sachet B contains:

Ascorbic acid	4.700 g
Sodium ascorbate	5.900 g

On reconstitution in 1 litre of water one sachet A and one sachet B provide:

Sodium	181.6 mmol/l
Chloride	59.8 mmol/l
Sulphate	52.8 mmol/l
Potassium	14.2 mmol/l
Ascorbate	29.8 mmol/l

#### 3. LIST OF EXCIPIENTS

Also contains aspartame (E951). Contains a source of phenylalanine. May be harmful for people with phenylketonuria.



**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for oral solution in sachets.  
(Single treatment of four sachets)

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

Use before date: {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

Store below 25°C. The solution may be stored for up to 24 hours at room temperature or in the fridge (2°C - 8°C).

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Norgine BV, Hogehilweg 7, 1101CA Amsterdam ZO, The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)****13. BATCH NUMBER**

Batch No:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

To be completed nationally.

**15. INSTRUCTIONS ON USE**

**Dissolve the contents of one sachet A and one sachet B with one litre of water.**

**16. INFORMATION IN BRAILLE**

*Braille on the carton – mock up*  
*“MOVIPREP”*

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

Sachet A

**1. NAME OF THE MEDICINAL PRODUCT**

MOVIPREP

Powder for oral solution in sachets.

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each sachet A contains:

Macrogol 3350	100 g
Sodium sulphate	7.500 g
Sodium chloride	2.691 g
Potassium chloride	1.015 g

On reconstitution in 1 litre of water one sachet A and one sachet B provide:

Sodium	181.6 mmol/l
Chloride	59.8 mmol/l
Sulphate	52.8 mmol/l
Potassium	14.2 mmol/l
Ascorbate	29.8 mmol/l

**3. LIST OF EXCIPIENTS**

Sachet A also contains aspartame (E951). Contains a source of phenylalanine. May be harmful for people with phenylketonuria.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for oral solution in sachets.  
(Single treatment of four sachets)

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use.  
Dissolve the contents of Sachet A and Sachet B in one litre of water.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Read the package leaflet before use.

Store below 25°C. The solution may be stored for up to 24 hours at room temperature or in the fridge (2°C - 8°C).

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

Sachet B

**1. NAME OF THE MEDICINAL PRODUCT**

MOVIPREP

Powder for oral solution in sachets.

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each sachet B contains:

Ascorbic acid	4.700 g
Sodium ascorbate	5.900 g

On reconstitution in 1 litre of water one sachet A and one sachet B provide:

Sodium	181.6 mmol/l
Chloride	59.8 mmol/l
Sulphate	52.8 mmol/l
Potassium	14.2 mmol/l
Ascorbate	29.8 mmol/l

**3. LIST OF EXCIPIENTS**

Sachet A also contains aspartame (E951). Contains a source of phenylalanine. May be harmful for people with phenylketonuria.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for oral solution in sachets.  
(Single treatment of four sachets)

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use.

Dissolve the contents of Sachet A and Sachet B in one litre of water.**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Read the package leaflet before use.

Store below 25°C. The solution may be stored for up to 24 hours at room temperature or in the fridge (2°C - 8°C).

## Module 5

### Scientific discussion during initial procedure

#### *Executive Summary*

#### **Introduction**

After reviewing data on quality, safety and efficacy, the MHRA granted a National Marketing Authorisation to Norgine Limited for Moviprep on 19<sup>th</sup> January 2006 (PL 0322/0084). This Public Assessment Report is based on the Assessment Report for a Mutual Recognition Procedure (MRP) marketing authorisation application for Moviprep (powder for oral solution), made under Directive 2001/83/EC (as amended), Article 10b with the UK as Reference Member State. The Concerned Member States were Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, The Netherlands, Spain and Sweden. The MRP was completed on the 2<sup>nd</sup> October 2006 with no withdrawals. The Marketing Authorisation was then transferred to the present Marketing Authorisation Holder, Norgine B.V. on 31/10/2006.

Moviprep is indicated for bowel cleansing prior to any clinical procedures requiring a clean bowel, eg, bowel endoscopy, radiology or digestive tract surgery.

The main active ingredient of Moviprep is Macrogol 3350. This high molecular weight polyethylene glycol has been shown to exert an osmotic effect that influences fluid transfer through the colon mucosa. Macrogol 3350 maintains an iso-osmotic liquid flow throughout the length of the gastrointestinal tract. The other ingredients in Moviprep are sodium sulphate anhydrous, sodium ascorbate and Vitamin C (ascorbic acid). It is claimed that ascorbic acid is a non-toxic substance with a high osmotic property and a pleasant taste.

#### **Development Programme**

Moviprep was developed to provide:

- A bowel preparation that required less volume of formulated solution to be ingested than currently marketed formulations.
- A product that was as efficacious as existing bowel preparations.
- A product that was more palatable than existing bowel preparations.

The addition of ascorbic acid to macrogol 3350 and sodium sulphate anhydrous enables the necessary osmotic load to be delivered in a 2-litre volume. Due to the hypertonicity of the solution, more water would need to be ingested after each dose. The absence of sodium bicarbonate, due to its chemical incompatibility with ascorbic acid, will result in a loss of base reserve, which is restored by replacing the appropriate amount of ascorbic acid with sodium ascorbate.

Much of the Moviprep development is borne out of experience with Norgine's product Movicol (PL 00322/0070), a powder formulation for the treatment of chronic constipation and faecal impaction. Movicol has a number of ingredients common to Moviprep (macrogol 3350, sodium chloride, potassium chloride, and the sweetener acesulfame potassium), and it is manufactured at the same site.

### **General comments on compliance with GMP, GLP, GCP and agreed ethical principles**

No new preclinical studies were conducted, which is acceptable given that the major ingredients are those of the original product Movicol (PL 00322/0070) which was granted UK approval in December 1995.

Clinical studies on Moviprep were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that Moviprep provides satisfactory clinical benefits.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.



## QUALITY ASPECTS

This is a pharmacy only product indicated for bowel cleansing prior to any clinical procedures requiring a clean bowel e.g. bowel endoscopy, radiology, or digestive tract surgery, for individuals aged 18 years and over. A course of treatment consists of two doses of Moviprep. One dose consists of one Sachet A and one sachet B dissolved together in one litre of water. This solution should be drunk over a period of one to two hours. This is then repeated with a second dose of Moviprep. Both sachets are contained in a single bag, and one pack of Moviprep contains a single treatment of two bags.

### Formulation

The active ingredients are packaged as dry powders in two separate sachets that are then emptied into a litre of water for reconstitution of the final preparation.

Sachet A contains:

- 100g macrogol 3350
- 7.500g sodium sulphate, anhydrous
- 2.691g sodium chloride
- 1.015g potassium chloride
- Excipients: aspartame, acesulfame potassium, lemon flavouring

Sachet B contains:

- 4.700g ascorbic acid
- 5.900g sodium ascorbate

A satisfactory Expert Report was provided on the Quality part of the dossier (Module 3).

### Drug Substance - Macrogol 3350

Macrogol is commonly used as an excipient in a number of pharmaceutical products. In Moviprep, macrogol is regarded as an active ingredient. Macrogol is subject of a Certificate of Suitability. Written confirmation from the active ingredient manufacturer (AIM) was provided that the applicant would be informed of any changes in the manufacturing process.

Norgine carries out routine in-house particle size analysis on batches received.

### Drug Substance – Sodium Sulphate, Anhydrous

The material is an inorganic active, and controlled according to the Ph.Eur. monograph. There is written confirmation from the AIMs of sodium sulphate, anhydrous that they will inform the applicant of any changes made to the manufacturing process of the active ingredient. A DMF for sodium sulphate from each AIM was submitted with the application.

The range of tests and limits conform to the Ph.Eur requirements for sodium sulphate anhydrous. The specification also meets the requirements of ICH guidelines, with respect to specifications, residual solvents, and impurities. The applicant has provided satisfactory justification for the specification.

The applicant states that there are no impurities besides those mentioned in the Ph.Eur. with regard to the starting materials and also no such impurities arising from the manufacturing

process of sodium sulphate anhydrous. Norgine carries out routine in-house particle size analysis on batches received. Satisfactory batch data in the form of Certificates of Analysis have been provided

### **Drug Substance – Sodium Chloride**

Sodium chloride is a common substance and is used as an excipient in a large number of pharmaceutical products, and is a common ingredient of food. The manufacturer has agreed to inform the applicant of any changes in the manufacturing process. The drug substance specification is based on the Ph.Eur. monograph. The drug substance complies with the requirements of the monograph. The range of tests and limits conform to the Ph.Eur requirements for sodium chloride.

There are no impurities besides the ones mentioned in the Ph.Eur. Also, there are no impurities (or related compounds) arising due to the manufacturing process of sodium chloride. Norgine carries out routine in-house particle size analysis (using sieve analysis) on batches received.

### **Drug Substance – Potassium Chloride**

The manufacturer confirmed by letter that they will inform the applicant of any changes in the manufacturing process.

The drug substance specification is based on the Ph.Eur. monograph. The drug substance complies with the requirements of the monograph. The range of tests and limits conform to the Ph.Eur. requirements for potassium chloride. The specification also meets the requirements of ICH guidelines, with respect to specifications and impurities. The applicant has provided satisfactory justification for the specification. The following potential impurities are not covered by the Ph.Eur. monograph: silicate (levels comply with USP) and nitrate. No organic substances are used in the manufacturing process and therefore organic volatile impurities are highly unlikely (levels comply with USP). It is concluded that the specification is satisfactory.

Norgine carries out routine in-house particle size analysis (using sieve analysis) on batches received. Analytical methodologies and appropriate validation data have not been provided, on the grounds that the methods used are the same as those described in the Ph.Eur. monograph. Satisfactory batch data in the form of Certificates of Analysis have been provided.

### **Drug Substance - Ascorbic Acid**

Ascorbic acid has a Certificate of Suitability and the active ingredient manufacturer has agreed to notify the Market Authorisation holder of any changes made to the manufacturing process.

### **Drug Substance - Sodium Ascorbate**

Sodium ascorbate is the subject of a Drug Master File that was assessed as part of this application.

## Drug Product

The product comprises two sachets (A and B), each made up of a laminate consisting of low density polyethylene, aluminium, and paper. One sachet A and one sachet B are wrapped together in a clear polypropylene pouch. Two such pouches are contained in one packet of Moviprep, and comprise the full course of treatment. Sachet B contains the ascorbic acid and sodium ascorbate, Sachet A contains the other ingredients.

Macrogol has been widely used as a non-absorbable osmotic agent for intestinal lavage. The addition of electrolytes produce a macrogol solution which is designed to ensure negligible net loss or gain of water, sodium, potassium, and bicarbonate.

The addition of ascorbic acid to macrogol 3350 and sodium sulphate anhydrous enables the necessary osmotic load to be delivered in a 2-litre volume. Due to the hypertonicity of the solution, more water would need to be ingested after each dose.

Much of the Moviprep development is borne out of experience with Norgine's product Movicol (PL 00322/0070), a powder formulation for the treatment of chronic constipation and faecal impaction. Movicol has a number of ingredients common to Moviprep (macrogol 3350, sodium chloride, potassium chloride, and the sweetener acesulfame potassium).

*Principal active ingredients with demonstrable effects on increasing stool volume and stool weight (osmotic laxatives):*

- Macrogol 3350
- Sodium sulphate, anhydrous
- Ascorbic acid
- Sodium ascorbate

*Ingredients classed as active and which are present for safety reasons only (in order to maintain electrolyte balance):*

- Sodium chloride
- Potassium chloride
- Also sodium ascorbate contributes to the total sodium content

*Excipients*

- Aspartame
- Acesulfame potassium
- Lemon flavouring

## Pharmaceutical Development

The Market Authorisation holder presented data from studies designed to justify the choice and amount of active ingredients and excipients used in Moviprep. Studies examined the effectiveness of different formulations in increasing stool weight and volume, the taste and acceptability of the preparation and the compatibility of ingredients. The data supported the levels of ingredients and method of formulation currently used for Moviprep.

**Manufacture**

A satisfactory description of the manufacturing process was described for Sachet A and Sachet B. Satisfactory in process controls were used for validation and evaluation of the manufacturing process. Satisfactory specifications for the drug product were provided. Batch formula and batch analysis data were provided for three pilot scale batches for Sachet A and one manufacturing scale batch for Sachet B. Satisfactory descriptions of methods of analysis and validation data for the Moviprep have been provided. Certificates of Analysis for three batches of Sachet A and Sachet B were provided and are acceptable.

**Container Closure System**

The Sachet material is the same for Sachet A and B. Satisfactory specification of the primary packaging were provided together with Certificates of Analysis.

**Stability**

Satisfactory stability data from three batches were provided. The data supported the shelf-life for each Sachet of 36 months. Further stability tests were carried out on Moviprep made into solution according to the instructions on the label. The results demonstrated that the solution was stable for 24 hours at 2-8°C or 25°C

### **NON-CLINICAL ASPECTS**

Moviprep is a new fixed combination product but some of the major ingredients are those of the original product Movicol (PL 00322/0070) which was granted UK approval in December 1995. Movicol is currently licensed and actively marketed in over 39 countries worldwide including nine countries within the European Union in which marketing authorisation was granted via the mutual recognition procedure in July 1996, with the UK as the reference member state.

No new preclinical data has been supplied with these applications and this is acceptable for this type of application and there are no preclinical objections to the granting of a Marketing Authorisation for this product.

## CLINICAL ASPECTS

### 1. INTRODUCTION

Moviprep is a new fixed combination product but some of the major ingredients are those of the original product Movicol (PL 00322/0070) which was granted UK approval in December 1995. Movicol is currently licensed and actively marketed in over 39 countries worldwide including nine countries within the European Union in which marketing authorisation was granted via the mutual recognition procedure in July 1996, with the UK as the Reference Member State.

### 2. BACKGROUND

The main active ingredient of Moviprep (as with Movicol) is Macrogol 3350. This high molecular weight polyethylene glycol has been shown to exert an osmotic effect that influences fluid transfer through the colon mucosa. Macrogol 3350 maintains an iso-osmotic liquid flow throughout the length of the gastrointestinal tract.

The other active ingredients in Moviprep are sodium sulphate anhydrous, sodium ascorbate and Vitamin C (ascorbic acid). It is claimed that ascorbic acid is a non-toxic substance with a high osmotic property and a pleasant taste.

Two pharmacodynamic studies and four clinical trials involving a total of over 700 subjects have been submitted to support the current application.

### 3. INDICATIONS

For bowel cleansing prior to any clinical procedures requiring a clean bowel e.g. bowel endoscopy, radiology or digestive tract surgery.

*Assessor's comment*

*This indication is appropriate.*

### 4. DOSE & DOSE SCHEDULE

These are satisfactory.

### 5. TOXICOLOGY

No new preclinical issues have been identified.

### 6. CLINICAL PHARMACOLOGY

#### 6.1 Pharmacodynamics

The high molecular weight macrogols are long linear polymers which retain water molecules by means of hydrogen bonds. When administered by the oral route, they lead to an increase in the volume of intestinal fluids. It is the volume of unabsorbed intestinal fluid which accounts for the laxative properties of the solution.

It is claimed that ascorbic acid is a non-toxic substance with a high osmotic property. Ascorbic acid is absorbed by the small bowel mucosa using sodium dependent carrier, which proves to be saturable, leading to an inverse relationship between ingested and absorbed dose.

The applicant has submitted two pharmacodynamic double-blinded studies involving healthy volunteers. The aim of these studies was to evaluate the effect of ascorbic acid when combined with sulphate-free Macrogol 3350 + electrolyte solution on stool weight and stool composition. The first study involved 5 subjects and the second study involved 30 subjects and included a dose-finding phase.

The first study showed that combining ascorbic acid (20g) and sodium sulphate (11.2g) increased the stool volume by 50% compared to the reference solution. The taste of the solution was considered acceptable. Despite no statistically significant differences among the preparations, the second study also showed that addition of ascorbic acid and sodium sulphate increased stool volume.

## **6.2 Pharmacokinetics**

Following oral ingestion, macrogol 3350 undergoes virtually no absorption from the gastrointestinal tract and passes unchanged through the gut. Any macrogol that may be 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 30mg and 180mg, an amount of about 70-85% of the dose is absorbed. Following oral intake of up to 12g ascorbic acid, it is known that only 2g 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.

## **6.3 Bioequivalence**

Not applicable.

## **7. EFFICACY**

Four clinical studies and one pilot study have been submitted in support of this application. These are summarised below. Moviprep is referred to by the code "NRL 994".

The first evidence for efficacy is based on the pilot study 98002 carried out with 7 healthy volunteers. This study established for the first time that high doses of ascorbic acid added to a standard Macrogol 3350 solution were able to increase the stool volume by 25%.

Norgine conducted four studies relating to safety and efficacy. The studies aimed to evaluate various aspects including efficacy and safety of this new oral cleansing solution. The four studies are summarised below.

**List of clinical efficacy studies**

Study ID	Country of study location	Design /Control type	Clinical phase	Study objective	Subjects recruited	No./Sex Median Age (yrs)	Primary endpoints
NRL994-02/2000	France	Pilot Monocentric open	II	Efficacy & safety	32	12M/18F 50.9	Overall quality of gut cleansing
NRL994-01/2000	Germany	Pilot Monocentric open	II	Efficacy & safety	36	18M/18F 49.2	Overall quality of gut cleansing
NRL994-01/2001	Germany	Randomised, Multicentric Single-blinded	III	Efficacy, safety & acceptability	362	150M/ 158F 58.8	Overall quality of gut cleansing
NRL994-02/2001	France	Randomised, Multicentric Single-blinded	III	Efficacy, safety & acceptability	352	181M/ 171F 53	Overall quality of gut cleansing

**Study NRL994-02/2000**

This was a monocentric, open non-comparative phase II study and the objective of this study was to investigate the efficacy and safety of this new oral gut cleansing solution (NRL994), in patients. The study was done on 30 patients (aged 18-65) submitted to colonoscopy.

The gut cleansing solution consisted of 2 litres of NRL 994. Preparation of the solution was made at the beginning of the afternoon, on the day preceding the colonoscopy. A nurse was in charge of the drug preparation and dispensing to the patient.

The primary endpoint was the quality of cleansing as judged by the investigator during colonoscopy using a grading score A-C established after assessment of the degree of colonic segment cleansing.

Each colonic segments cleansing was rated according to the following table:

Score	Rating	Definition
4	Very good	Only minor amount of fluid in the gut, but Easily removed by suction.
3	Good	Only smaller amounts of fluid stood in the gut, but easily removed by suction
2	Moderate	Fluid or semisolid remaining amounts of stool, most of it to be removed.
1	Bad	Fluid or semisolid remaining amounts of stool, most of it to be removed.
0	Very Bad	Colon full with remaining stool; colonoscopy incomplete or to be terminated in one of the pre-defined areas (rectum, sigmoid, descending, transverse or ascending colon).



The overall quality of bowel preparation was then determined using the following algorithm:

Classification	Definition
A	All colon segments clean (=scored 4 or 3)
B	At least one colon segment with residual amounts of stool (=scored 2 or 1)
C	At least one colon segment which cannot be examined because of the presence of remaining stool (=scored 0)

Grade A corresponded to very good (score 4) or good preparation (score 3) for all colon segments, B to a satisfactory preparation (at least one colon segment scoring 1 or 2), and C to a poor preparation with at least one colon segment with heavy hard stools (score 0). The colonoscopies were recorded and an independent endoscopist reviewed, *a posteriori*, the video tapes. The patient evaluation of the lavage solution taste was recorded on a VAS scale ranging from 0 mm (very bad) to 100 mm (excellent).

### Results

Out of the 32 patients enrolled, 30 were included in this study and underwent colonoscopy. They were 12 males and 18 females with a mean age of 51±11 years. The total amount of NRL994 ingested was 1950ml (range: 1000-2000ml) and the additional amount of extra water was 1026±249ml. Two patients failed to drink the test solution.

The investigator judged the quality of the bowel preparation to be good or very good in all colonic segments in 20 patients and at least in one segment moderate in 7, bad in 2 and very bad in 1. The final score was of 20A, 9B and 1C ratings.

Overall grading of the preparation according to the investigator:

Classification grade A to C	Protocol's qualification	Final grading
A = all segments grade 3-4	Very good or good	20
B= at least one segment grade 2	Moderate }	7
B= at least one segment grade 1	Bad }	2
C=at least one segment grade d)	Very Bad	1

Reviewer's and investigator's initial grading were concordant in 8 cases and discordant in 17 with differences attributed to the method of grading; during the scope progression (when assessed on video tape by the reviewer) instead of during the withdrawal after washing if needed (per endoscopic assessment by the investigator).

According to the protocol, a final assessment of 25 video tapes was done by the investigator using the same method and 6 patients were classified as grade A, 15 patients as grade B and 4 patients as grade C.

The digestive tolerance of the preparation was good (excellent or mild) in 26 patients (86.7%), moderate in 2 patients and poor in 2 patients. Only one patient experienced a profuse vomiting (500ml) related to the intake NRL994.

### **Study NRL994-01/2000**

This was a monocentric, open phase II study to investigate the efficacy and safety of the new oral gut cleansing solution NRL 994.

It was an open, uncontrolled investigation conducted in a group of in-patients scheduled for colonoscopy. Patients were enrolled one or two days in advance prior to endoscopic procedure. Gut cleansing started in the evening prior to the intervention when the first dose of NRL994 was taken; bowel preparation was continued in the morning of the day of colonoscopy when the second dose was taken. The patients' participation in the study ended after the endoscopic procedure.

36 patients were enrolled, of which 34 completed the study.

The study drug consisted of an oral administration of two doses of NRL994 each to be diluted in 1000ml of water.

Each dose of one litre had to be taken within one hour, followed by 500ml of clear fluid. The study drug was taken in two split doses with a nocturnal pause. The first dose was taken in the evening before the intervention and the second one in the morning of the day of colonoscopy.

#### *Results*

Colonoscopy was performed on 34 patients. In 32 patients (94.1%), the endpoint of colonoscopy was the ascending colon. Thirty-three of the endoscopic procedures were recorded on video tapes for subsequent assessment by an independent reviewer.

The investigator/endoscopist rated the degree of gut cleansing as very good (little fluid in the gut that is easily removed) or good (small amounts of fluid easily removed) in 88%, 76%, 79% and 75% of the patients in the rectum sigmoid, descending and transverse colon respectively. On the more proximal segment (ascending colon) the percentage of very good or good was slightly lower (59%) and moderate ratings (fluid or semisolid stools easily removed by suction) were achieved in 38% of patients. In only a few colon segments, quality of gut preparation was reported to be bad (fluid or semisolid stools that were partially removable). One very bad rating as assigned by the investigator.

The independent endoscopist based his assessment on the review of the video tapes and rated the degree of gut cleansing as very good to good in 91%, 94%, 88%, 84% and 84% of the five predefined gut segments from rectum to ascending colon.

The overall quality of cleansing was classified by the investigator as grade A in 14 patients (41.2%), as B in 19 patients (55.9%) and as C in 1 patient (2.9%). According to the independent reviewer 25 patients (78.1%) were classified as grade A, and 7 patients (21.9%) were grade B.

Overall tolerability of the gut lavage solution was considered to be excellent in 9 patients (26.5%), as mild in 19 patients (55.9%) and as moderate in 6 patients (17.7%).

### Study NRL 994-02/2001

This was a randomised, multicentre, single-blinded clinical phase III trial on 2 parallel treatment groups comparing the efficacy, safety and acceptability of NRL 994 versus a marketed colon preparation solution.

The study drug consisted of 2 litres of NRL 994. Each litre had to be drunk within an hour followed by at least 1000ml of any additional clear fluid.

The comparator (Fleet Phospho Soda<sup>®</sup> FPS) solution consisted of two flasks of 45 ml, which had to be dissolved into 125ml of water. Each intake was followed up with 250ml of clear drinks. A delay of at least 12 hours between the intake of the 2 x 45ml of FPS had to be observed. In addition, at least 750ml of clear fluids or more needed to be drunk between the two intakes.

Each colonic segment's cleansing was rated in a similar manner to that described in NRL 994 -02/2000.

#### Results

Three hundred and fifty two (352) patients, 181 males and 171 females mean age 53 years [51.71, 54.29] were enrolled in this study. The proportion of discontinuations and deviations from the protocol (NRL994 N=7 versus FPS with N=6) were low and balanced in each treatment group. These patients were excluded from all efficacy analysis.

Five patients who did not drink "at least ¾" of the test solution were excluded from the per protocol population. This per protocol population was subdivided into two sub groups: one in which the investigator's advice for each colonoscopy was available and one in which the video tape was available allowing an expert's assessment. Population included in ITT (patients who took at least ¼ of the study solution) and modified ITT (mITT) (patients who took at least ½ of the study solution) for the efficacy analyses were in fact identical.

Populations in each analysis:

Populations N patients (%)	NRL 994	FPS	Total	p
Randomised	175	177	352	
Excluded from all efficacy analysis	7 (4.00)	6 (3.39)	13 (3.69)	0.984
<b>Efficacy analyses:</b>				
ITT for efficacy (ITT)	168 (96.00)	171 (96.61)	339 (96.31)	0.762
Modified ITT (mITT)	168 (96.00)	171 (96.61)	339 (96.31)	0.762
Per protocol (PP investigators)	164 (93.71)	170 (96.05)	334 (94.89)	0.321
Per protocol (PP experts)	138 (78.86)	144 (81.36)	282 (80.11)	0.557

There were no significant differences between the colonoscopy procedures in the two treatment groups. Colonoscopies were performed between 08.00 hours and 16.00 hours, their mean duration was 22.6 minutes and the caecum was reached in 97% of

the cases. Six colonoscopies had to be performed again, due to insufficient preparation as asked for by the investigators.

For the 282 evaluable patients of the per protocol population (Experts' PP population), the clinical success rate of the two preparations was 72.46 % in the NRL994, versus 63.89% in the FPS group. With a clinical equivalence bound of 15%, this difference leads to a conclusion that NRL994 was at least equivalent to FPS, with an observed advantage for NRL994 over FPS of +8.57%. [-2.25% + 19.40%].

Clinical success of the solution by the expert (PP population)	NRL 994	FPS	ALL
	N(%)	N(%)	N(%)
Success	100 (72.46%)	92 (63.89%)	192 (68.09%)
Failure	38 (27.54%)	52 (36.11%)	90 (31.91%)
Total evaluable (expert)	138	144	282 (100.00%)
Difference NRL 994 – FPS [two-sided 95% C.I.] +8.57% [-2.25%, + 19.40%]			
Video unavailable	26 (15.85%)	26 (15.29%)	52 (15.57%)

The conclusion for equivalence was confirmed with the investigator assessment on the investigators' PP population. The observed difference was: -2.54% [-12.44%, + 7.36%]

This study demonstrated as primary end point that the quality of colonic preparations involving NRL994 was at least equivalent to that of FPS with 72.5% and 63.9% of successful gut cleansing respectively. The acceptability profile presented some significant advantages of NRL994 compared with FPS, particularly improved patient comfort.

### Study NRL 994-01/2001

This was a randomised, multi-centric, single blinded, pivotal phase III trial to assess the efficacy, safety and acceptability of the 2 litre gut cleansing solution NRL994 versus a standard colon preparation of PEG 3350 and sodium sulphate plus electrolytes (Klean Prep)

The objective of the study was to demonstrate that NRL994 was not less effective than the gold standard comparator, with regards to the overall quality of bowel preparation in patients undergoing colonoscopy.

Treatment with NRL994 comprised two doses of one litre each. This powder dose was diluted to a litre with water and was followed by an additional intake of 500ml of clear liquid. The first dose in the afternoon or evening before the colonoscopy was taken until 22:00hrs and the second dose in the following morning of the colonoscopy (from 06:00hrs onwards). A time interval of at least one hour was required between the end of intake and the start of colonoscopy.

The comparator was 4 doses of 1 litre each of Klean Prep solution. The powder of each dose was diluted to one litre of water and had to be drunk within an hour (250ml per 15mins). Two doses were taken in the afternoon or evening before the colonoscopy (until 22:00hrs) and a further two doses in the morning before the

colonoscopy (from 05:00hrs onwards). A time interval of at least one hour was required between the end of intake and start of colonoscopy.

### *Results*

The success rates for gut cleansing (grade A + B) were 88.9% in the NRL994 group and 94.8% in the Klean Prep group. The lower limit of the one-sided 97.5% confidence interval for the rate difference of -5.9% was calculated to be -12.0%. Since this value was greater than the pre-specified value of -15%, non-inferiority of NRL994 versus PEG+E was demonstrated.

Based on the video tape reviews, the independent expert panel rated the degree of gut cleansing as very good or good in the five predefined segments from rectum to ascending colon in the NRL 994 group (58.2%, 51.7%, 47.8%, 49.1% and 38%). Similarly for the Klean Prep group, the results were 62.8%, 58.7%, 54.9%, 47.7% and 35.5%. These percentages were slightly higher in the Klean Prep group.

The overall use of the gut lavage solution was rated as good in about 50% of patients, independent of whether they were assessed by expert panel or the colonoscopist.

Mean degree of gut cleansing by averaging all segmental scores in each of the two treatment groups was  $2.5 \pm 0.5$  in the NRL group and  $2.5 \pm 0.4$  in the Klean Prep group.

Global quality of gut cleansing assessed on a 100mm VAS scale was comparable in both treatment groups.

The overall easiness to perform colonoscopy was rated by the investigator on 3-level VRS scale and was easy to perform in more than 50% of all patients.

Several post hoc subgroup analyses were performed. The results indicated that NRL994 was effective in all age groups as well as patients with renal impairment, presence of cardiovascular diseases or inflammatory bowel disease (IBD).

This study was conducted versus a gold standard large volume preparation in patients undergoing colonoscopy. The patients consistently and statistically preferred NRL994 over Klean Prep on the basis of several acceptability parameters. Both treatment groups were safe and generally well tolerated. NRL994 proved to be equally safe and effective as the established gold standard Klean Prep.

### ***Assessor's comment***

*Over 800 patients were investigated regarding the effectiveness of Moviprep. Although the criteria of efficacy used were not consistent across all the studies, these are acceptable clinical parameters. The efficacy of Moviprep was demonstrated in all the studies presented.*

## **8. SAFETY**

A review of the published safety data are included in this submission. No new safety issues have been identified.

The incidences of adverse events in the studies submitted for this application are summarised in the tables below.

### Reported Common Adverse Events

Body System/ Adverse Events*	Study NRL994- 02/2000  (N=30)	Study NRL994- 01/2000  (N=34)	Study NRL994- 01/2001  (N=352)		Study NRL994- 02/2001  (N=340)	
	NRL994	NRL994	NRL994	PEG+E	NRL994	FPS
Malaise	-	-	36	35		
Muscle cramps	-	-	-	-	-	1
Vomiting	4	2	13	22	3	
Nausea	-	1	27	40		
Dyspepsia			5	5		
Abdominal pain	-	1	24	30		
Stomach pain			4	4		
Other	-	1	-	-	2	18

*Other significant adverse events*

The data showed no reports of any other significant adverse events.

**Analysis of adverse events by organ system or syndrome incidence of adverse events in individual studies on ITT populations (by patient analysis)**

Body System/Adverse Events	Study N00/01 Ancillary+	Study NRL994 - 02/2000	Study NRL994-01/2000	Study NRL994-01/2001		Study NRL994-02/2001 <sup>1</sup>	
		NRL994	NRL994	NRL994	PEG +E	NRL994	FPS
No. of Subject	10	30	34	352		340	
Body as whole							
Dizziness/Hypotension	-	-	-	-	-	1§	-
Malaise	-	-	-	35	36	-	-
Thirst sensation	5	-	-	-	-	-	-
Muscle cramps	-	-	-	-	-	-	1
Cardiovascular	-	-	-	-	-	-	-
Gastrointestinal							
Vomiting	-	4	2	13	22	3	-
Nausea	-	-	1	27	40	-	-
Rectal bleeding	-	-	1§	-	-	1§	-
Dyspepsia	-	-	-	5	5	-	-
Anal pain	-	-	-	-	-	1	1
Abdominal Pain	1	-	1	24	30	-	-
Stomach pain	-	-	-	4	4	-	-
Other	-	1	-	-	-	-	-
Metabolic and Nutritional disorder	-	8	-	-	-	1	22
Serious Adverse Events	-	1*	1§	-	-	-	3
<b>TOTAL</b>	<b>6</b>	<b>13</b>	<b>6</b>	<b>99</b>	<b>128</b>	<b>7</b>	<b>25</b>

N.B. One subject could be present in one or more adverse event.

\* This was a low potassium plasma level which existed prior to intake of NRL-994.

§ Unrelated to NRL994.

+ Concerned only NRL994 eg Candidate D<sup>+</sup> extra water in the ancillary arm.

- No case observed.

<sup>1</sup>In the Phase III Pivotal study NRL994-02/2001, in contrast to the NRL994-01/2000 study, the clinical symptoms (tolerance assessment) documented by the patients via the questionnaire where not systematically classified as AE, thus explaining the difference of incidence between the two studies.

**Assessor's comments**

*As expected, almost all reported adverse events involve the gastrointestinal system. The majority of reported adverse events are well known with this class of osmotic laxatives (nausea, vomiting and abdominal pain).*

**9. EXPERT REPORT**

A satisfactory clinical expert report has been provided with appropriate CV.

**10. SUMMARY OF PRODUCT CHARACTERISTICS**

Satisfactory.

**11. PATIENT INFORMATION LEAFLET**

Satisfactory.

**12. LABELLING**

This appears satisfactory.

**13. DISCUSSION**

Osmotic laxatives, including macrogols (polyethylene glycols), have been available in the European Union, including the UK for much more than 10 years. Their use is well established with recognised efficacy and acceptable safety. The addition of ascorbic acid appears to confer some advantage in terms of increased stool volume.

With regards to the current application, sufficient clinical information has been submitted. When used as indicated, Moviprep has a favourable benefit-to-risk ratio. The hazard associated with Moviprep appears to be low and acceptable when considered in relation to its therapeutic benefits.

**14. CONCLUSION**

A Marketing Authorisation was granted.



## OVERALL CONCLUSIONS

The Pharmaceutical and Medical Assessments resulted in a positive risk/benefit assessment and a Market Authorisation was granted.

**MODULE 6****STEPS TAKEN AFTER AUTHORISATION**

The following non-confidential variations have been approved since the granting of the market authorisation

Type	Date	Purpose
COA	31/10/2006	Change of ownership to Norgine BV
Med II	10/04/2007	Update SPC
Med II	23/03/2007	Update UK licence after MRP