Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Mutual Recognition Procedure

MOVIPREP POWDER FOR ORAL SOLUTION
PL 20142/0005; UK/H/0891/001/MR

Macrogol 3350, sodium sulfate anhydrous, sodium chloride, potassium chloride, ascorbic acid, sodium ascorbate

Norgine BV

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Moviprep Powder for Oral Solution (PL 20142/0005; UK/H/0891/001/MR). It explains how Moviprep Powder for Oral Solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Moviprep Powder for Oral Solution, patients should read the Package Leaflet or contact their doctor or pharmacist.

What is Moviprep Powder for Oral Solution and what is it used for?
Moviprep Powder for Oral Solution is a 'new fixed combination' product, containing Macrogol 3350, anhydrous sodium sulfate, sodium chloride, potassium chloride, ascorbic acid and sodium ascorbate.

Moviprep Powder for Oral Solution is used to make your bowels clean so that they are ready for examination, e.g. by bowel endoscopy or radiology.

How does Moviprep Powder for Oral Solution work
Moviprep Powder for Oral Solution works by emptying the contents of your bowel, so you should expect watery bowel movements.

The active ingredients are contained in two separate sachets:

- Sachet A contains 100 g macrogol 3350, 7.500 g sodium sulfate anhydrous, 2.691 g sodium chloride and 1.015 g potassium chloride.
- Sachet B contains 4.700 g ascorbic acid and 5.900 g sodium ascorbate

When these sachets are made up to one litre of solution the solution contains 181.6 mmol of sodium, 52.8 mmol sulfate, 59.8 mmol chloride, 14.2 mmol potassium and 29.8 mmol ascorbate. This product also contains aspartame which is a source of phenylalanine. This may be harmful to people with phenylketonuria.

How is Moviprep Powder for Oral Solution used?
The treatment can be taken as either divided or single doses, as described below:

- Divided doses: one litre of Moviprep in the evening before and one litre in the early morning of the day of the procedure.
- Single dose: two litres in the evening before the clinical procedure or two litres in the morning of the clinical procedure.

For the divided dose and the single dose taken in the evening before the procedure, there should be at least one hour between the end of intake of fluid (MOVIPREP or clear liquid) and the start of the colonoscopy. For the single dose taken the morning of the procedure, there should be at least two hours between the end of intake of Moviprep and at least one hour between the end of intake of any clear liquid and the start of the colonoscopy.

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

When taking Moviprep you should continue to take plenty of fluids. The fluid content of Moviprep does not replace your regular liquid intake.

Please read Section 3 of the Package Leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

This medicine can only be obtained from pharmacies and is intended for use by healthcare professionals only.

How has Moviprep Powder for Oral Solution been studied?
Clinical studies in patients have shown that Moviprep Powder for Oral Solution is at least as effective as other currently marketed solutions for clearing the bowels.

What are the possible side effects of Moviprep Powder for Oral Solution?
The possible side effects observed with Moviprep Powder for Oral Solution are the same as those observed with other marketed solutions for clearing the bowels. Very common side effects (affecting more than 1 user in 10) are abdominal pain, abdominal distension, tiredness, feeling generally unwell, soreness of the anus, nausea and fever. Other common side effects (affecting up to 1 in 10 people) are hunger, problems sleeping, dizziness, headache, vomiting, indigestion, thirst and chills.

For further information, please see Section 4 the Package Leaflet.

Why is Moviprep Powder for Oral Solution approved?
It was concluded that, in accordance with EU requirements, Moviprep Powder for Oral Solution is effective at cleansing the bowels prior to any clinical procedure requiring a clean bowel, with a suitable side-effect profile that was similar to other marketed products. The benefit-risk profile for this product was considered to be favourable and a product licence was granted.

What measures are being taken to ensure the safe and effective use of Moviprep Powder for Oral Solution?
A risk management plan (RMP) has been developed to ensure that Moviprep Powder for Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics, and the package leaflet for Moviprep Powder for Oral Solution includes the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Moviprep Powder for Oral Solution
The UK granted a marketing authorisation for Moviprep Powder for Oral Solution on 19 January 2006. Following a mutual recognition procedure that concluded on 02 October 2006, Austria, Belgium, Germany, Denmark, Spain, Finland, France, Ireland, Italy, Luxembourg, the Netherlands and Sweden agreed to grant a marketing authorisation for Moviprep Powder for Oral Solution.

The full PAR for Moviprep Powder for Oral Solution follows this summary.

For more information about treatment with Moviprep Powder for Oral Solution, read the Package Leaflet or contact your doctor or pharmacist.

This summary was last updated in October 2015.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Moviprep Powder for Oral Solution (PL 20142/0005; UK/H/0891/001/MR) could be approved.

This product is a pharmacy medicine intended for use by healthcare professionals for bowel cleansing prior to any clinical procedures requiring a clean bowel, e.g. bowel endoscopy, radiology or digestive tract surgery.

This application was granted under Article 10b of Directive 2001/83/EC, as amended, as a new fixed combination of six existing active substances, macrogol 3350, anhydrous sodium sulfate, sodium chloride, potassium chloride, ascorbic acid and sodium ascorbate.

The RMS for these procedures was the UK and the CMSs were Austria, Belgium, Germany, Denmark, Spain, Finland, France, Ireland, Italy, Luxembourg, the Netherlands and Sweden.

No new non-clinical studies were conducted, which is acceptable given that the application is for a product containing a new fixed combination of six well-known active substances.

Since this product will be used in place of other products that are currently on the market and contains six well-known active substances that are highly stable with a very low toxic potential, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is not deemed necessary.

Two double-blind pharmacodynamics studies were submitted to support this application. Both studies, performed on healthy volunteers, were designed to evaluate the concept of the effect of ascorbic acid when combined with sulfate-free macrogol 3350 + electrolyte solution on stool weight and stool composition.

In addition, the following five efficacy studies were submitted with this application:

- A pilot study to establish the effects of high doses of ascorbic acid on stool volume
- Two pilot studies to investigate the efficacy and safety of Moviprep Powder for Oral Solution
- Two studies comparing Moviprep Powder for Oral Solution with other marketed bowel cleansing products.

All studies were conducted in line with current Good Clinical Practice.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of the product.

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.

A satisfactory Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application.

A national licence was granted in the UK on 19 January 2006. Following a mutual recognition procedure that concluded on 02 October 2006, Austria, Belgium, Germany,

Denmark, Spain, Finland, France, Ireland, Italy, Luxembourg, the Netherlands and Sweden considered that the application could be approved.

II QUALITY ASPECTS

II.1 Introduction

This application was were made under Article 10b of Directive 2001/83/EC, as amended, a new fixed combination of six existing active substances, macrogol 3350, anhydrous sodium sulfate, sodium chloride, potassium chloride, ascorbic acid and sodium ascorbate.

Moviprep Powder for Oral Solution is a powder formulation contained in two paper/low-density polyethylene/aluminium/low-density polyethylene sachets, containing 112 g of powder (Sachet A, containing macrogol 3350, anhydrous sodium sulfate, sodium chloride and potassium chloride) and 11 g of powder (Sachet B, containing ascorbic acid and sodium ascorbate). Both sachets are contained in a transparent bag. One pack of Moviprep Powder for Oral Solution contains a single treatment of two bags. Pack sizes consist of 1, 10, 40, 80, 160 and 320 packs of single treatment. Not all pack sizes may be marketed.

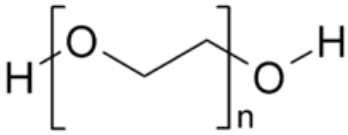
One pack of Moviprep Powder for Oral Solution, consists of 100 g macrogol 3350, 7.500 g sodium sulfate anhydrous, 2.691 g sodium chloride, 1.015 g potassium chloride, 4.700 g ascorbic acid and 5.900 g sodium ascorbate. In addition to these active substances, Moviprep Powder for Oral Solution also contains the excipients aspartame (E951), potassium acesulfame (E950) and lemon flavouring (consisting of maltodextrin, citral, lemon oil, lime oil, xanthan gum and vitamin E).

The drug product is compatible with water. When reconstituted, the drug product makes an opaque/yellow solution.

II.2 DRUG SUBSTANCE

Macrogol 3350

INN/Ph.Eur name: Macrogol 3350
Structural formula:

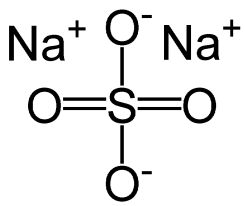


Molecular formula: $H-(OCH_2-CH_2)_n-OH$

Appearance: White or almost white solid with a waxy or paraffin-like appearance.
Solubility: Very soluble in water and in methylene chloride, very slightly soluble in alcohol, practically insoluble in fatty oils and in mineral oils.

Sodium sulfate anhydrous

INN/Ph.Eur name: Sodium sulfate anhydrous
Structural formula:



Molecular formula: Na_2SO_4

Appearance: White or almost white solid with a waxy or paraffin-like appearance
Solubility: Freely soluble in water

Molecular weight: 142.04

Sodium chloride
INN/Ph.Eur name: Sodium chloride
Molecular formula: NaCl

Appearance: White, crystalline powder or colourless crystals or white pearls
Solubility: Freely soluble in water, practically insoluble in ethanol.

Molecular weight: 58.4

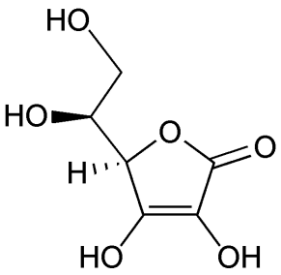
Potassium chloride
INN/Ph.Eur name: Potassium chloride

Molecular formula: KCl

Appearance: White or almost white crystalline powder or colourless crystals.
Solubility: Freely soluble in water, and practically insoluble in anhydrous ethanol.

Molecular weight: 74.6

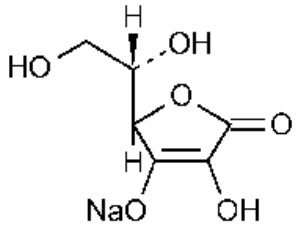
Ascorbic Acid
INN/Ph.Eur name: Ascorbic Acid
Chemical name: (2R)-2-[(1S)-1,2-dihydroxyethyl]-4,5-dihydroxyfuran-3-one
Structural formula:



Molecular formula: $C_6H_8O_6$

Appearance: White or almost white crystalline powder or colourless crystals.
Solubility: Freely soluble in water, soluble in alcohol, and practically insoluble in ether.
Molecular weight: 176.13

Sodium Ascorbate
INN/Ph.Eur name: Sodium Ascorbate
Chemical name: sodium 2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate
Structural formula:



Molecular formula: $C_6H_7NaO_6$

Appearance: White or almost white crystalline powder or colourless crystals.
Solubility: Freely soluble in water, and practically insoluble in anhydrous ethanol.

Molecular weight: 198.1

Macrogol 3350, sodium sulfate anhydrous, sodium chloride, potassium chloride, ascorbic acid, sodium ascorbate all comply with their European Pharmacopoeia monographs.

All aspects of the manufacture of the active substances macrogol 3350, potassium chloride, ascorbic acid and sodium ascorbate from its starting materials are controlled by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

Appropriate retest periods have been proposed for each active substance based on stability data submitted for the active substances.

Appropriate specifications are provided for the active substances, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided that comply with the proposed specifications.

Appropriate proof-of-structure data have been supplied for the active substances. All potential known impurities have been identified and characterised. Suitable Certificates of Analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substances to be physically and chemically stable drugs, and supporting appropriate retest periods.

II.3 DRUG PRODUCT

Pharmaceutical development

The objective of the development programme was to produce a “fixed combination” product containing the active substances containing macrogol 3350, anhydrous sodium sulfate, sodium chloride, potassium chloride, ascorbic acid and sodium ascorbate that has a suitable efficacy/safety profile for use in patients.

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of lemon flavouring, which is controlled to a suitable in-house specification.

No excipients of animal or human origin are used in the final product. None of the excipients are sourced from genetically modified organisms.

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale and has shown satisfactory results. Appropriate in-process controls are in place at suitable points during manufacture.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years with the storage conditions "Store in the original package" and "Do not store above 25°C" are acceptable. The shelf-life after reconstitution is 24 hours. The solution may be refrigerated, but the solution should be covered.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of the active substances are well-established. As all active substance are widely used and well-known, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is, thus, appropriate.

Since this product will be used in place of other products that are currently on the market and contains six well-known active substances that are highly stable with a very low toxic potential, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is not deemed necessary.

IV CLINICAL ASPECTS
IV.1 Introduction
Two double-blind pharmacodynamics studies were submitted to support this application. Both studies, performed on healthy volunteers, were designed to evaluate the concept of the effect of ascorbic acid when combined with sulfate-free macrogol 3350 and electrolyte solution, on stool weight and stool composition.

In addition, the following five efficacy studies were submitted with this application:
- A pilot study to establish the effects of high doses of ascorbic acid on stool volume
- Two pilot studies to investigate the efficacy and safety of Moviprep Powder for Oral Solution
- Two studies comparing Moviprep Powder for Oral Solution with other marketed bowel cleansing products.

All studies were conducted in line with current Good Clinical Practice.

IV. 2 Pharmacokinetics

No new studies have been submitted and none are required.

IV.3 Pharmacodynamics

The applicant has submitted two pharmacodynamic double-blind studies involving healthy volunteers. The aim of these studies was to evaluate the concept of the effect of ascorbic acid when combined with sulfate-free Macrogol 3350 and electrolyte solution, on stool weight and stool composition.

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

IV.4 Clinical efficacy

Four clinical studies and one pilot study have been submitted in support of this application. These are summarised below.

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	II	Efficacy & Safety	36	18M 18F 49.2	Overall quality of gut cleansing
NRL994-01/2001	Germany	Randomised, Multicentric	III	Efficacy, Safety & acceptability	362	150M/ 158 58.8	Overall quality of gut cleansing
NRL994-02/2001	France	Randomised, Multicentric	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 performed in 30 patients (aged 20-65) 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 end point 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 segment 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 stool 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, partially removable.
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 (=score 0)

Grade A corresponded to very good (score 4) or good preparation (score 3) for all colon segments, grade B to a satisfactory preparation (at least one colon segment scoring 1 or 2), and grade 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 videotapes. The patient evaluation of the lavage solution taste was recorded on a VAS scale ranging from 0 (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 $\pm$ 11 years. The total amount of NRL994 ingested was 1950ml (range: 1000-2000 ml) and the additional amount of extra water was 1026$\pm$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 rating.

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 0	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 videotapes 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.

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 500 ml 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 videotapes 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 videotapes 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 grade B in 19 patients (55.9%) and as grade C in one 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 sodium phosphate solution, consisted of two flasks of 45 ml, which had to be dissolved in 125 ml of water. Each intake was followed up with 250 ml of clear drinks. A delay of at least 12 hours between the intake of the 2 x 45 ml of sodium phosphate had to be observed. In addition, at least 750 ml of clear fluids or more needed to be drunk between the two intakes.

Results
Three hundred and fifty two 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 sodium phosphate 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 videotape was available allowing an expert's assessment. Population included in intent to treat (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**	**Sodium phosphate**	**Total**	**p**
Randomised	175	177	352	
Excluded from all efficacy analysis	7 (4.00)	6 (3.39)	13 (3.69)	0.984
Efficacy analyses:				
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 sodium phosphate group. With a clinical equivalence bound of 15%, this difference lead to the conclusion that NRL994 was at least equivalent to sodium phosphate, with an observed advantage for NRL994 over sodium phosphate of +8.57% [-2.25% + 19.40%].

Clinical success of the solution by the expert (PP population)	**NRL 994**	**Sodium phosphate**	**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 – Sodium phosphate [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 sodium phosphate with 72.5% and 63.9% of successful gut cleansing, respectively. The acceptability profile presented some significant advantages of NRL994 compared with sodium phosphate, 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 macrogol 3350 and sodium sulfate plus electrolytes.

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.

Results

The success rates for gut cleansing (grade A + B) were 88.9% in the NRL994 group and 94.8% in the macrogol plus electrolytes 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%, of NRL994 versus macrogol +E was demonstrated.

Based on the videotape 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

macrogol plus electrolytes group, the results were 62.6%, 58.7%, 54.9%, 47.7% and 35.5%. These percentages were slightly higher in the macrogol plus electrolytes 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 macrogol plus electrolytes 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 a 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 in 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 macrogol plus electrolytes 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 macrogol plus electrolytes.

IV.5 Clinical Safety

A review of the published safety data is 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	Macrogol +E	NRL994	Sodium phosphate
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 in individual studies is below.

Body System/Adverse Events	Study N00/01 Ancillary+	Study NRL994-02/2000	Study NRL994-01/2000	Study NRL994-01/2001		Study NRL994-02/2001[1]	
		NRL994	NRL994	NRL994	Macrogol +E	NRL994	Sodium phosphate
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
TOTAL SUBJECTS	6	13	6	99	128	7	25

N.B. one subject may have more than one adverse event

*, this was a low potassium plasma level which pre-existed prior to intake of NRL-994; §, unrelatd to NRL994; +, concerned only NRL994 eg Candidate D^+ extra water in the ancillary arm; -, no case observed

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 were not systematically classified as adverse effects (AE), thus explaining the difference of incidence between the two studies.

IV.6 Risk Management Plan (RMP)

The Marketing Authorisation Holder has submitted an RMP in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Moviprep Powder for Oral Solution.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V User consultation

A user consultation with target patient groups on the patient information leaflet (PIL) has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI Overall conclusion, benefit/risk assessment and recommendation

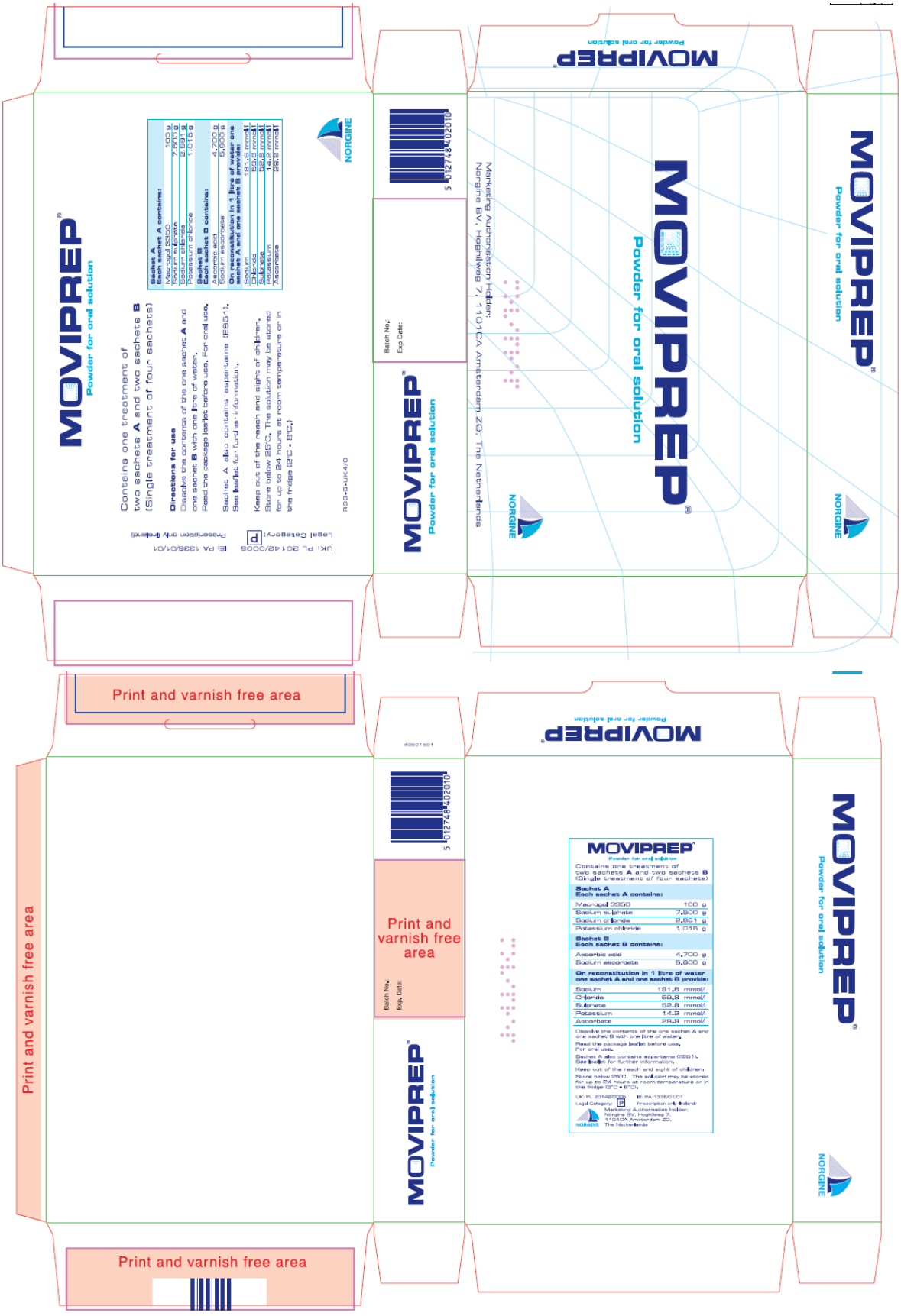
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The application includes an adequate review of published non-clinical data concerning the active substances. Over 800 patients were investigated regarding the effectiveness of Moviprep Powder for Oral Solution. The efficacy of Moviprep Powder for Oral Solution was demonstrated in all the studies presented.

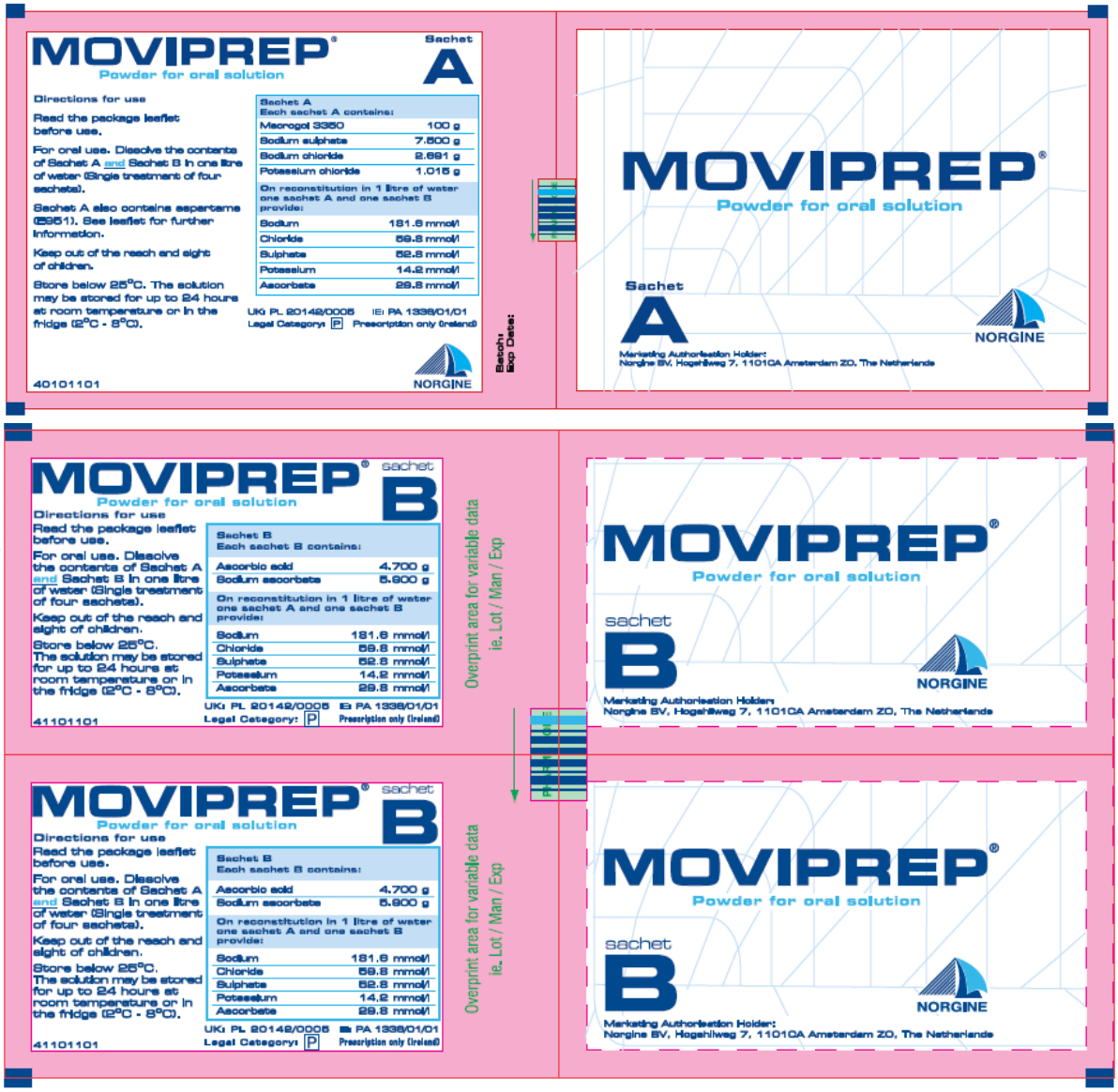
As expected, almost all reported adverse events involve the gastrointestinal system. The majority of reported adverse events are well known with this class of osmotic laxatives (nausea, vomiting and abdominal pain). The adverse events observed with Moviprep Powder for Oral Solution are consistent with those observed with other products of this kind.

The benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), PIL and labelling are satisfactory with the data collected and consistent with other similar products. In accordance with Directive 2012/84/EU, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

The currently approved labels are presented below:


MOVIPREP®
Powder for oral solution
Contains one treatment of two sachets A and two sachets B (Single treatment of four sachets)
Directions for use
Dissolve the contents of the one sachet A and one sachet B with one litre of water.
Read the package leaflet before use. For oral use.
Sachet A also contains aspartame (E951).
See leaflet for further information.
Keep out of the reach and sight of children.
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).
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 181.8 mmol/l
Chloride 59.8 mmol/l
Sulphate 52.8 mmol/l
Potassium 14.2 mmol/l
Ascorbate 29.8 mmol/l
NORGINE
Batch No:
Exp Date:
5 012748 402010
Marketing Authorisation Holder:
Norgine BV, Hoghiltweg 7, 1101CA Amsterdam ZO, The Netherlands
Print and varnish free area
Print and varnish free area
Print and varnish free area


MOVIPREP®
Powder for oral solution
Sachet A
Directions for use
Read the package leaflet before use.
For oral use. Dissolve the contents of Sachet A and Sachet B in one litre of water (Single treatment of four sachets).
Sachet A also contains aspartame (E951). See leaflet for further information.
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Chloride 59.8 mmol/l
Sulphate 52.8 mmol/l
Potassium 14.2 mmol/l
Ascorbate 29.8 mmol/l
UK: PL 20142/0005 IE: PA 1336/01/01
Legal Category: P Prescription only (Ireland)
40101101
NORGINE
Batch:
Exp Date:
MOVIPREP®
Powder for oral solution
Sachet
A
NORGINE
Marketing Authorisation Holder:
Norgine BV, Hogehilweg 7, 1101CA Amsterdam ZO, The Netherlands
MOVIPREP®
Powder for oral solution
sachet
B
Directions for use
Read the package leaflet before use.
For oral use. Dissolve the contents of Sachet A and Sachet B in one litre of water (Single treatment of four sachets).
Keep out of the reach and sight of children.
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).
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
UK: PL 20142/0005 IE: PA 1336/01/01
Legal Category: P Prescription only (Ireland)
41101101
Overprint area for variable data
ie. Lot / Man / Exp
MOVIPREP®
Powder for oral solution
sachet
B
NORGINE
Marketing Authorisation Holder:
Norgine BV, Hogehilweg 7, 1101CA Amsterdam ZO, The Netherlands
MOVIPREP®
Powder for oral solution
sachet
B
NORGINE
Marketing Authorisation Holder:
Norgine BV, Hogehilweg 7, 1101CA Amsterdam ZO, The Netherlands

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	**Procedure number**	**Product information affected**	**Date of start of the procedure**	**Date of end of procedure**	**Approval / non approval**	**Assessment report attached Y/N (version)**
To update the SmPC and PIL in line with the CCDS.	UK/H/0891/001/II/044	SmPC/PIL	29/08/2014	07/07/2015	Approval	Yes
To update the SmPC to include a warning regarding fluid intake, to update adverse reactions and to correct any typographical errors. Consequentially, the leaflet has been updated.	UK/H/0891/001/II/047	SmPC/PIL	01/04/2015	30/09/2015	Approval	Yes

Annex I

Reference:	PL 20142/0005-0064 (UK/H/0891/001/II/044)
Product:	Moviprep Powder for Oral Solution
Marketing Authorisation Holder:	Norgine BV.
Active Ingredients:	Macrogol 3350, sodium sulfate anhydrous, sodium chloride, potassium chloride, ascorbic acid, sodium ascorbate
Reason:	To update the SmPC and PIL in line with the CCDS

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

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

The Applicant proposes to submit changes to Section 4.2 of the SmPC and consequential changes to the PIL as a result of the recent update of the Company Core Data Sheet (CCDS) in relation to posology.

Supporting Evidence
The texts involved in the proposed changes are highlighted in the attached SmPC and PIL.

Assessor's Comment
The proposed changes to section 4.2 of the SmPC and the corresponding changes to the text of the PIL are acceptable as they do not materially alter the dosing recommendations of the previous SmPC. In addition the applicant has made minor editorial alterations to the PIL in the current submission. These latter changes are also satisfactory.

Conclusion
The grant of this variation is recommended.

Decision - Granted
Date - 07 July 2015

Annex 2

Reference:	PL 20142/0005-0068 (UK/H/0891/001/II/047)
Product:	Moviprep Powder for Oral Solution
Marketing Authorisation Holder:	Norgine BV.
Active Ingredients:	Macrogol 3350, sodium sulfate anhydrous, sodium chloride, potassium chloride, ascorbic acid, sodium ascorbate
Reason:	To update sections 2, 4.4, 4.8, 5.1 and 5.3 of the SmPC to include a warning regarding fluid intake, to update adverse reactions and to correct any typographical errors. Consequentially, the leaflet has been updated.

Background
The Applicant proposes to update section 4.4 (Special warnings and precautions for use) of the SmPC to include an additional warning regarding fluid intake, as follows:

"The fluid content of MOVIPREP® when reconstituted with water does not replace regular fluid intake and adequate fluid intake must be maintained."

The applicant also proposes to revise the text regarding adverse reactions in Section 4.8 of the SmPC (Undesirable effects) and to update sections 2, 5.1 and 5.3 to change 'sulphate' to its INN name 'sulfate'.

Consequentially the applicant also proposes to update the PIL to reflect the changes to the SmPC.

Supporting Evidence
A revised PIL and SmPC have been provided.

Assessor's Comment
The proposed changes to section 4.4 and 4.8 of the SmPC are acceptable as they do not materially alter the texts of the previous SmPC.

Conclusion
The grant of this variation is recommended.

Decision - Granted
Date - 30 September 2015