HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

23 September 2009

MOVIPREP powder for oral solution
Pack of 1 containing 2 bags, each with 1 sachet of 122 g of powder A and 1 sachet of 11 g of powder B (CIP: 378 816-4)

Applicant: NORGINE PHARMA

Macrogol 3350 + ascorbic acid

ATC code: A06AD65

Marketing authorisation date: March 9, 2007

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients

Sachet A

Macrogol 3350	100.000 g
Sodium sulphate anhydrous	7.500 g
Sodium chloride	2.691 g
Potassium chloride	1.015 g

Sachet B

Ascorbic acid	4.700 g
Sodium ascorbate	5.900 g

Electrolyte concentration after dissolving sachet A and sachet B in one litre of solution

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

Each sachet A contains 0.233 g of aspartame.

1.2. Indication

“MOVIPREP is a solution administered orally, for bowel cleansing prior to any examination requiring a clean bowel (e.g. bowel endoscopy or radiology).”

1.3. Dosage

“Adults and the elderly:
The treatment involves drinking two litres of Moviprep solution. It is also advisable to drink one litre of clear liquid (water, clear soup, fruit juice without pulp, soft drinks, tea and/or coffee without milk).
To obtain one litre of Moviprep, dissolve together 1 sachet A and 1 sachet B in one litre of water. This solution should be drunk over a period of one to two hours.
Repeat to obtain a 2nd litre of Moviprep.
This preparation can be taken as follows:
• either in 2 intakes, one litre of Moviprep the evening before the examination and one litre early in the morning on the day of the examination.
• or in one intake, two litres of Moviprep the evening before the examination.

The last glass of fluid (Moviprep or drink) must be drunk at least one hour before the examination.
No solid foods should be eaten from the start of preparation to the end of the examination.

Children:
No studies have been conducted in the paediatric population.
Moviprep is therefore not recommended for patients under 18 years of age.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

A : Alimentary tract and metabolism
A06 : Laxatives
A06A : Laxatives
A06AD : Osmotic laxatives
A06AD65 : Macrogol, combinations

2.2. Medicines in the same therapeutic category

Directly comparable medicines are combination macrogol-based laxatives used in colonic preparation:
- BIOPEG oral solution
- COLOPEG powder for oral solution
- FORTRANS powder for oral solution
- KLEAN PREP powder for oral solution

2.3. Medicines with a similar therapeutic aim

Other products indicated for preparation for endoscopy and radiology examinations:
- FLEET PHOSPHO-SODA oral solution
- PREPACOL (for colonic examinations only) film-coated tablet and oral solution (not reimbursed)
- X PREP oral powder.

3 ANALYSIS OF AVAILABLE DATA

The application submitted by the company includes 4 comparative MOVIPREP studies:
- One phase III non-inferiority study vs KLEAN-PREP (study NRL 994-01/2001)
- One phase IV superiority study vs COLOPEG (NORMO study)
- Two phase III studies vs FLEET PHOSPHO-SODA, one equivalence study (NRL 994-02/2001) and a superiority study (NRL 994-01/2004).

3.1. Efficacy

The 4 studies were of similar methodology. The studies were conducted single-blind. The primary endpoint of the 4 studies was the percentage of colonoscopies conducted successfully (based on the Harefield scale), i.e. the overall efficacy of the colonic preparation assessed by experts using video footage.

The Harefield scale is defined as follows:
Initially each of the 5 predefined colonic segments (rectum, sigmoid colon, descending colon, transverse colon and ascending colon) is scored 0 to 4:
4 : segment empty and clean
3 : presence of clear, yellow or green liquid
2 : presence of brown liquid or small semisolid stools that can be fully moved or removed by suction, enabling a comprehensive examination of the underlying mucous membrane
1 : stools that are semisolid or than can be partially moved/removed by suction, risk of incomplete examination of underlying mucous membrane
0 : large quantity of solid matter preventing interpretation of the segment's examination and/or causing the colonoscopy to be terminated

Then an overall score (A to D) is calculated based on the individual scores obtained:
A : excellent preparation = all segments are clean (5 scores of 3, 4),
B : good preparation = at least 1 segment containing brown liquid or residue that can be fully moved or removed by suction (score of 2), without influencing the colonoscopy results,
C : mediocre preparation = at least 1 segment obtaining a score of 1,
D : poor preparation = at least 1 segment obtaining a score of 0.

A successful colonic preparation, and therefore colonoscopy, was defined as scores A or B and an unsuccessful one as C or D.

The treatment's acceptability for the patient was a secondary endpoint.

Treatment methods: on the evening before and/or on the day of the colonoscopy, patients took the product given to them for the colonoscopy, following the administration methods of the colonic preparation, treatment and recommended food intake. The colonoscopy was scheduled for the next morning.

Results:

Study NRL 994-01/2001[1]

It is a phase III randomised, single-blind, non-inferiority study that aims to demonstrate the efficacy of MOVIPREP (2 litres administered in fractioned amounts with a break overnight) is not inferior to that of KLEANPREP (4 litres administered in fractioned amounts with a break overnight) in hospital patients aged 18 to 85, scheduled for a morning colonoscopy.
It was possible to conclude that the product was not inferior if the lower unilateral 97.5% confidence interval limit of the difference in efficacy levels remained to the right of the – 15% limit.

The intention-to-treat (ITT) population comprised 359 patients (180 in the MOVIPREP group and 179 in the KLEANPREP group) and the per-protocol (PP) population, 308 patients (153 patients in the MOVIPREP group and 155 in the KLEANPREP group).
Nine patients withdrew from the study early (of which 8 before the start of the colonoscopy): 5 in the MOVIPREP group and 4 in the KLEANPREP group. The most frequent reason was the occurrence of adverse events (n=5): 3 in the MOVIPREP group and 2 in the KLEANPREP group. Twenty-two patients in the MOVIPREP group and twenty in the KLEANPREP group were excluded for a major breach of protocol (insufficient patient compliance and/or endoscopic images not recorded).

The PP population characteristics for the MOVIPREP group were as follows: 51.6% men and 48.4% women. The mean age was 58.8 +/- 15.4 years. Over 50% of patients were aged 60 or more. The most common reasons for colonoscopy were abdominal pain (35.1%), presence of blood in the stools (22.1%) and routine check-up (15.9%).
In the PP population, the colonic preparation was effective, defined by the success rate (scores A and B), for 88.9% of the MOVIPREP group (136/153) and 94.8% of the KLEANPREP group (147/155). The difference in success scores for MOVIPREP and KLEANPREP was -5.9% (97.5%CI = [-12%; ∞]). MOVIPREP was therefore not inferior to KLEANPREP.
The colonic preparation's taste was assessed using a questionnaire as a secondary endpoint. 47.1% of patients in the MOVIPREP group and 21.3% of patients in the KLEANPREP group deemed the preparation's taste to be generally "acceptable" ($p<0.025$).
Among the patients treated with MOVIPREP, 73.9% had no trouble drinking all the solution, compared to 53.1% of those treated with KLEANPREP ($p<0.05$).

NORMO study

This phase IV randomised, single-blind superiority study compared two groups: one given MOVIPREP and the other given COLOPEG. The patients included had to be aged 18 to 85 and treated as outpatients.
The patients were given either MOVIPREP (2 litres) or COLOPEG (4 litres) according to SPC-compliant administration methods.

Four hundred patients were included. The demographic characteristics were similar in the two ITT groups, with 47% women and 53% men. The mean age was 55.1 in the MOVIPREP group and 55.9 in the COLOPEG group.
The most common reasons for colonoscopy were screening for colorectal cancer (59.50%), abdominal pain (23.75%) and presence of blood in the stools (22.50%).
In the ITT population, the colonic preparation was effective, defined by the success rate (scores A or B on the Harefield scale) assessed by experts, for 94.1% of the MOVIPREP group and 90.9% of the COLPEG group (+3.15% difference; 95%CI = [-2.5; 8.8], NS).
The entire solution was drunk by 85.4% of MOVIPREP patients and by 80.95% of COLOPEG patients; 87% of patients would take MOVIPREP again and 52% would take COLPEG again ($p<0.001$).

1 Ell C, Fischbach W, Bronisch HJ, Dertinger S, et Al. Randomized trial of low-volume PEG solution versus standard PEG + electrolytes for bowel cleansing before colonoscopy. Am J Gastroenterol. 2008;103(4):883-93

NORCOL study (study NRL994-02/2001)[2]
Phase III randomised, single-blind equivalence study to compare the efficacy of 2 litres of MOVIPREP administered the evening before the colonoscopy to that of 2x45 ml of FLEET PHOSPHO-SODA (sodium phosphate solution) administered the evening before the colonoscopy to hospitalised patients or outpatients aged 18 to 75. It was possible to conclude that the two products were equivalent if the lower bilateral 95% confidence interval limit of the difference in the efficacy level did not exceed 15%.

The PP population comprised 282 patients. The colonic preparation was effective, defined by the success rate (scores A or B on the Harefield scale) assessed by experts, for 72.5% of the MOVIPREP group and 63.9% of the FLEET PHOSPHO-SODA group.
The difference between MOVIPREP and FLEET PHOSPHO-SODA was +8.6% (95%CI: [-2.3%; +19.4%]). With a clinical equivalence limit set at 15% by the protocol, the difference observed led to the conclusion that the MOVIPREP colonic solution was at least equivalent to FLEET PHOSPHO-SODA.
After MOVIPREP treatment, 82% of patients were prepared to take the same preparation again and 73.6% after treatment with FLEET PHOSPHO-SODA. Patients were surveyed by a nurse the morning before the colonoscopy using a questionnaire.

Study NRL 994-01/2004
Phase III randomised superiority study to compare the efficacy of MOVIPREP administered as a fractioned dose with a break overnight to that of FLEET PHOSPHO-SODA administered the evening before the colonoscopy to patients aged 18 to 85 scheduled for an outpatient colonoscopy to screen for colorectal cancer.

The colonic preparation was effective, defined by the success rate (scores A or B on the Harefield scale) assessed by experts, for 93% of the MOVIPREP group and 23% of the FLEET PHOSPHO-SODA group ($p<0.0001$).
After MOVIPREP treatment, 88% of patients were prepared to take the same preparation again and 78% after treatment with FLEET PHOSPHO-SODA (statistically significant difference). Patients were surveyed over the phone within 7 days of the colonoscopy.

3.2. Safety

Study NRL 994-01/2001
Out of 359 ITT population patients, 44% (159/359) suffered from at least one adverse event (AE): 40.6% (73/180) of patients treated with MOVIPREP and 47.8% (86/179) of patients treated with KLEANPREP.
Most AE were mild to moderate. Only one severe AE was reported for the MOVIPREP group: abdominal pain commencing around 1 ½ hours after the first dose of treatment (of which 90% was taken). The investigator deemed this AE to be probably attributable to treatment. The pain resolved spontaneously after 3.5 hours without treatment.
In both treatment groups, the most frequent AEs observed were gastrointestinal disorders (34.3%) [see table 1]. In addition, 19.8% of patients (n=71) suffered from malaise: 19.4% of patients (n=35) in the MOVIPREP group and 20.1% of patients in the KLEANPREP group (n=36). The type of malaise was not specified.
The percentage of patients with at least one AE attributable to treatment was 83% (71/86) in the KLEANPREP group and 93% (68/73) in the MOVIPREP group.

[2] Bitoun A, Ponchon T, Barthet M, et Al Norcol Group. Results of a prospective randomised multicentre controlled trial comparing a new 2-L ascorbic acid plus polyethylene glycol and electrolyte solution vs. sodium phosphate solution in patients undergoing elective colonoscopy. Aliment Pharmacol Ther. 2006;24:1631-42

Table 1: Number of patients with AE (frequency ≥ 1%)

	MOVIPREP	KLEANPREP
Nausea	27 (15.0%)	40 (22.3%)
Abdominal pain	24 (13.3%)	30 (16.8%)
Vomiting	13 (7.2%)	22 (12.3%)
Dyspepsia	5 (2.8%)	5 (2.8%)

NORMO study
The percentage of patients developing at least one AE attributable to treatment was significantly lower in the MOVIPREP group than in the COLOPEG group. 77.72% compared to 87.37%.
In both groups, the most frequent AEs observed were gastrointestinal disorders (83.3%), i.e. abdominal distension (58.3%), anal discomfort (55.8%), nausea (42%), abdominal pain (32.8%) and vomiting.
Anal discomfort was less frequent in the MOVIPREP group: 47.52% of patients compared to 59.09%.
The labwork obtained from blood samples before and after the colonoscopy showed:
- a higher increase in chloride ions in the MOVIPREP group (Δ=1.66 compared to Δ=0.96 in the COLOPEG group).
- a decrease in the concentration of carbonate ions in the MOVIPREP group (Δ =-1.59) compared to an increase in the COLPEG group (Δ=0.60).

NORCOL study (study NRL994-02/2001)
In the MOVIPREP group, 4.1% (7/169) of patients had at least one AE compared to 14.6% (25/171) given FLEET PHOSPHO-SODA.
Ten patients in the FLEET PHOSPHO-SODA group suffered from hypokalaemia and none in the MOVIPREP group; 12 patients suffered from hyperphosphataemia in the group treated with FLEET PHOSPHO-SODA and none in the MOVIPREP group.

Study NRL 994-01/2004
The percentage of AE deemed to be definitely attributable to treatment was 34.7% in the FLEET PHOSPHO-SODA group and 28.8% in the MOVIPREP group. As expected, blood sodium and phosphates increased in the FLEET PHOSPHO-SODA group while sodium decreased and phosphates remained steady in the MOVIPREP group.

3.3. Conclusion

The efficacy of MOVIPREP was evaluated in 3 phase III studies compared to KLEANPREP or FLEET PHOSPHO-SODA and one phase IV study compared to COLOPEG. The efficacy assessment was based the preparation's success rate (scores A or B on the Harefield scale).
MOVIPREP's success rate was:
- similar to COLOPEG (94.1% compared to 90.9%, p>0.05),
- not inferior to that of KLEANPREP (89.9% compared to 94.8%),
- superior to that of FLEET PHOSPHO-SODA in a superiority study (93% compared to 23%). It should be noted that in this study the very low success rate of FLEET PHOSPHO-SODA does not correspond to levels usually encountered.
- equivalent to FLEET PHOSPHO-SODA in an equivalence study (72.5% compared to 63.9%).

The most common adverse events in both groups were nausea, abdominal pain, anal discomfort, and ion disorders in similar proportions in the two groups.

The preparation's acceptability for the patient and therefore the quality of the colonic preparation, in addition to the competency of the endoscopist, determine the success of the colonoscopy[3]. Due to the limits of the methods, which are difficult to avoid (single-blind, short time between the colonoscopy and patient questionnaire), the studies presented cannot lead to the conclusion that MOVIPREP is more acceptable (secondary endpoint) than the other colonic preparations.

MOVIPREP 2 litres (+ 1 litre of water or clear liquid) appears to be similar in terms of efficacy to the 4 litre solutions of PEG. Compared to FLEET PHOSPHO-SODA, there does not appear to be any difference in preparation in the best study conducted. The product therefore has the theoretical advantage of comprising only 2 litres of preparation + 1 litre of water or clear liquid but does not prove better efficacy or better acceptability compared to the 4 litre PEG solutions or FLEET PHOSPHO-SODA.

[3] SFED recommendations September 2007

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

It is necessary to clean the colon to prepare patients before an endoscopy or radiology examination and colonic surgery.

The condition's severity is determined by the results of the examination.

The efficacy/adverse effects ratio in this indication is high.

This product is for first-line therapy.

Alternatives are available.

> Public health benefit: colonoscopies are indicated for diagnostic purposes for patient monitoring or to screen for precancerous or cancerous lesions in patients at risk.
> The improvement in colorectal cancer screening alone (a condition representing a major burden) is a public health priority (Public health act 2004).
>
> In light of clinical trial data, MOVIPREP has not demonstrated that it can improve the detection of lesions beyond the available alternatives, particularly in screening.
>
> Consequently, MOVIPREP is not expected to provide an additional benefit to public health in this indication.

The actual benefit of this product is substantial.

4.2. Improvement in actual benefit

In the absence of the proof of superiority for MOVIPREP compared to other colonic preparations, MOVIPREP does not provide any further improvement in actual benefit for digestive endoscopies (IAB V). MOVIPREP is an additional useful diagnostic tool.

4.3. Therapeutic use

It is necessary to clean the colon to prepare patients before an endoscopy[4] or radiology examination.

It should be noted that colorectal cancer screening has been identified as a public health priority in France[5]. For patients at a high or very high risk, screening for colorectal cancer and precancerous lesions currently relies on colonoscopies, which are the standard examination of the colonic mucous membrane, preceded by colonic cleansing.
In subjects at a moderate risk (general population), mass screening using the Hemoccult test followed by a colonoscopy when the results are positive, has proved effective in reducing colorectal cancer mortality[6].

[4] ANAES guidelines April 2004: lower GI endoscopy: indications outside population screening
[5] Bretagne J, Faivre J. La Société Française de Gastro-entérologie recommande la mise en place d'un dépistage généralisé et organisé du cancer colorectal en France. Gastroentérol Clin Biol 2000;24:492-3
[6] Importance of virtual colonoscopy in colorectal cancer screening ANAES 2001

MOVIPREP has the same therapeutic use as other polyethylene glycol (PEG)-based solutions specifically prescribed for bowel cleansing in adults prior to endoscopy or radiology examinations.

4.4. Target population

It is estimated that in France 1.1 to 1.2 million colonoscopies are conducted each year[7]. This estimate could be similar to the target population for MOVIPREP.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by the National Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and at the dosages in the MA.

4.5.1. Packaging: appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 65%

[7] Canard JM, Acta endoscopica, 2007, Lettre de la SFED, 2 jours d'endoscopie en France, résultats de l'enquête 2006