

Public Assessment Report

Movicol Chocolate 13.9g sachet, powder for oral solution

**Macrogol 3350
Sodium chloride
Sodium hydrogen carbonate
Potassium chloride**

UK/H/0131/004/DC

Norgine Limited

LAY SUMMARY

On 21st August 2008, the MHRA granted Norgine Limited a Marketing Authorisation (licence) for the medicinal products Movicol Chocolate 13.9g sachet, powder for oral solution (PL 00322/0086). These are products to be supplied through pharmacies and promoted to healthcare professionals only (P) that act as a laxative for the treatment of constipation in adults, adolescents and the elderly.

Movicol Chocolate helps you have a comfortable bowel movement even if you have been constipated for a long time. Movicol Chocolate also works in very bad constipation called faecal impaction.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Movicol Chocolate 13.9g sachet, powder for oral solution outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Movicol Chocolate 13.9g sachet, powder for oral solution
Type of Application	Decentralised Procedure
Active Substance	Macrogol 3350 Sodium chloride Sodium hydrogen carbonate Potassium chloride
Form	Powder for oral solution
Strength	13.125g Macrogol 3350 0.3507g Sodium chloride 0.1785g Sodium hydrogen carbonate 0.0317g Potassium chloride
MA Holder	Norgine Limited, Chaplin House, Widewater Place, Moorhall Road, Harefield, UB9 6NS
RMS	UK
CMS	Austria, Belgium, Finland, Ireland, and Sweden
Procedure Number	UK/H/0131/004/DC
MA Number	PL 00322/0086
Timetable	Day 180: 4 th August 2008

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

MOVICOL Chocolate 13.9g sachet, powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of MOVICOL Chocolate contains the following active ingredients:

Macrogol 3350	13.1250g
Sodium Chloride	0.3507g
Sodium Hydrogen Carbonate	0.1785g
Potassium Chloride	0.0317g

The content of electrolyte ions per sachet when made up to 125 ml of solution is as follows:

Sodium	65 mmol/l
Chloride	51 mmol/l
Potassium	5.4 mmol/l
Hydrogen Carbonate	17 mmol/l

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution. White to light brown free flowing powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of chronic constipation in adults and children above the age of 12. MOVICOL Chocolate is also effective in resolving faecal impaction, defined as refractory constipation with faecal loading of the rectum and/or colon.

4.2 Posology and method of administration

Chronic Constipation

A course of treatment for constipation with MOVICOL Chocolate does not normally exceed two weeks, although this can be repeated if required.

As for all laxatives, prolonged use is not usually recommended. Extended use may be necessary in the care of patients with severe chronic or resistant constipation, secondary to multiple sclerosis or Parkinson's Disease, or induced by regular constipating medication, in particular opioids and antimuscarinics.

Adults, adolescents and elderly: 1-3 sachets daily in divided doses, according to individual response. For extended use, the dose can be adjusted down to 1 or 2 sachets daily.

Children under 12 years of age: Not recommended. Alternative MOVICOL products are available for children.

Faecal impaction

A course of treatment for faecal impaction with MOVICOL Chocolate does not normally exceed 3 days.

Adults, adolescents and the elderly: 8 sachets daily, all of which should be consumed within a 6 hour period.

Children under 12 years of age: Not recommended. Alternative MOVICOL products are available for children.

Patients with impaired cardiovascular function: For the treatment of faecal impaction the dose should be divided so that no more than two sachets are taken in any one hour.

Patients with renal insufficiency: No dosage change is necessary for treatment of either constipation or faecal impaction.

Administration

Each sachet should be dissolved in 125ml water. For use in faecal impaction 8 sachets may be dissolved in 1 litre of water.

4.3 Contraindications

Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, ileus, severe inflammatory conditions of the intestinal tract, such as Crohn's disease and ulcerative colitis and toxic megacolon.

Hypersensitivity to the active ingredients or to any of the excipients.

4.4 Special warnings and precautions for use

Diagnosis of impaction/ faecal loading of the rectum should be confirmed by physical or radiological examination of the abdomen and rectum.

If patients develop any symptoms indicating shifts of fluid/electrolytes (e.g. oedema, shortness of breath, increasing fatigue, dehydration, cardiac failure) MOVICOL Chocolate should be stopped immediately and electrolytes measured, and any abnormality should be treated appropriately.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical interactions with other medicinal products have been reported. Macrogol raises the solubility of medicinal products that are soluble in alcohol and relatively insoluble in water (i.e. substances that have a hydrophilic and a hydrophobic pole in their molecular structure). There is therefore a theoretical possibility that the absorption of such medicinal products could be transiently reduced.

4.6 Pregnancy and lactation

There is no experience of the use of MOVICOL Chocolate during pregnancy and lactation and it should only be used if considered essential by the physician.

4.7 Effects on ability to drive and use machines

MOVICOL Chocolate has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The frequency of adverse reactions to MOVICOL from post marketing data is defined using the following MEDRA convention:

Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Adverse reactions to MOVICOL are very rare.

- Gastrointestinal disorders
Very rare: Abdominal pain attributable to the expansion of the contents of the intestinal tract, diarrhoea which usually responds to dose reduction, flatulence, vomiting, nausea,
- Immune system disorders
Very rare: allergic reactions, allergic rash, anaphylactic events,
- Skin and subcutaneous tissue disorders
Very rare: pruritis, exanthema

4.9 Overdose

Severe pain or distension can be treated by nasogastric aspiration. Extensive fluid loss by diarrhoea or vomiting may require correction of electrolyte disturbances.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Osmotically acting laxatives

ATC code: A06A D65

Macrogols are long linear polymers, also known as polyethylene glycols

Macrogol 3350 acts by virtue of its osmotic action in the gut, which induces a laxative effect. Macrogol 3350 increases the water content and hence the stool volume, which triggers colon motility via

neuromuscular pathways. The physiological consequence is an improved propulsive colonic transportation of the softened stools and a facilitation of the defaecation. Electrolytes combined with macrogol 3350 are exchanged across the intestinal barrier (mucosa) with serum electrolytes and excreted in faecal water without net gain or loss of sodium, potassium and water.

For the indication of faecal impaction controlled comparative studies have not been performed with other treatments (e.g. enemas). In a non-comparative study in 27 adult patients, MOVICOL (parent product) cleared the faecal impaction in 12/27 (44%) after 1 day's treatment; 23/27 (85%) after 2 days' treatment and 24/27 (89%) at the end of 3 days.

Clinical studies in the use of MOVICOL (parent product) in chronic constipation have shown that the dose needed to produce normal formed stools tends to reduce over time. Many patients respond to between 1 and 2 sachets a day, but this dose should be adjusted depending on individual response.

5.2 Pharmacokinetic properties

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

5.3 Preclinical safety data

Preclinical studies provide evidence that macrogol 3350 has no significant systemic toxicity potential, although no tests of its effects on reproduction or genotoxicity have been conducted.

There are no long-term animal toxicity or carcinogenicity studies involving macrogol 3350, although there are toxicity studies using high levels of orally administered high molecular macrogols that provide evidence of safety at the recommended therapeutic dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acesulfame Potassium (E950)

Chocolate Flavour (contains maltodextrin, acacia gum E414, vegetable oils and fats, propylene glycol E1520, and ethyl alcohol)

6.2 Incompatibilities

None are known.

6.3 Shelf life

3 years

Reconstituted solution: 6 hours.

6.4 Special precautions for storage

Sachet: Do not store above 25°C.

Reconstituted solution: Store at 2-8°C (in a refrigerator and keep covered).

6.5 Nature and contents of container

Sachet: laminate consisting of four layers: low density polyethylene, aluminium, low density polyethylene and paper.

Pack sizes: boxes of 20 or 30 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused solution should be discarded within 6 hours.

7 MARKETING AUTHORISATION HOLDER

Norgine Ltd,
Chaplin House, Widewater Place,
Moorhall Road,
Harefield, Uxbridge,
Middlesex, UB9 6NS,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00322/0086

- 9** **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY**
21/08/2008
- 10** **DATE OF REVISION OF THE TEXT**
21/08/2008

Module 3



Patient Information Leaflet

MOVICOL® CHOCOLATE

13.9g sachet, powder for oral solution

Read all of this leaflet carefully before taking your medicine.

This medicine is available without prescription. However, you still need to take MOVICOL Chocolate carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

If you need the information on this leaflet to be supplied in an alternative format, such as large print, please ring from the UK: 0800 198 5000.

In this leaflet:

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

1. What is MOVICOL Chocolate and what is it used for?
The name of this medicine is MOVICOL Chocolate 13.9g sachet, powder for oral solution. It is a laxative for the treatment of constipation in adults, adolescents and elderly. It is not recommended for children below 12 years of age.

MOVICOL Chocolate helps you to have a comfortable bowel movement even if you have been constipated for a long time. MOVICOL Chocolate also works in very bad constipation called faecal impaction.

2. Before you take MOVICOL Chocolate

Do not take MOVICOL Chocolate if your doctor has told you that you have:

- a blockage in your intestine (gut obstruction, ileus)
- a perforated gut wall
- severe inflammatory bowel disease like ulcerative colitis, Crohn's disease or toxic megacolon
- an allergy to any of the ingredients

Take special care with MOVICOL Chocolate

Heart conditions

Follow the special instructions in section 3 if you are taking MOVICOL Chocolate for faecal impaction.

Taking other medicines

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines including medicines obtained without a prescription.

Taking MOVICOL Chocolate with food or drink

This medicine can be taken any time with or without food and drink.

Pregnancy and breast feeding

If you are pregnant or breast feeding talk to your doctor before taking MOVICOL Chocolate.

Driving and using machines

MOVICOL Chocolate does not affect your ability to drive or use machines.

3. How to take MOVICOL Chocolate

Constipation:

A dose of MOVICOL Chocolate is 1 sachet.

Take this 1–3 times a day according to the severity of your constipation.

Faecal impaction:

A dose of 8 sachets a day of MOVICOL Chocolate is needed for the treatment of faecal impaction. The 8 sachets should be taken within 6 hours for up to 3 days if required. If you have a heart condition do not take more than 2 sachets in any one hour.

How to mix:

Open the sachet and pour the contents into a glass. Add about 125ml or 1/4 pint of water to the glass. Stir well until all the powder has dissolved and the MOVICOL Chocolate solution is clear or slightly hazy, then drink it. If you are taking MOVICOL Chocolate for faecal impaction it may be easier to dissolve 8 sachets in 1litre of water.

Duration of treatment

Constipation:

Treatment with MOVICOL Chocolate usually lasts for about 2 weeks.

If your constipation is caused by an illness such as Parkinson's disease or multiple sclerosis (MS), or if you take medicines that cause constipation your doctor may recommend that you take MOVICOL Chocolate for longer than 2 weeks.

Usually for long term treatment the dose can be lowered to either 1 or 2 sachets a day.

Faecal impaction:

Treatment with MOVICOL Chocolate can be for up to 3 days.

If you take more MOVICOL Chocolate than you should

You may develop diarrhoea. Stop taking MOVICOL Chocolate until it clears, and then start again at a lower dose. If you are worried contact your doctor or pharmacist.

If you forget to take MOVICOL Chocolate

Take the dose as soon as you remember to take it.

4. Possible side effects

Like all medicines, MOVICOL Chocolate can have side effects.

Tell your doctor immediately and stop taking MOVICOL Chocolate if:

- You feel weak, increasingly tired, breathless, very thirsty with a headache or get puffy ankles.
- You have a skin rash or itching which may be signs of an allergic reaction. Other possible signs of an allergic reaction include difficulty in breathing or dizziness.

Other side effects that you may have include:

Very rare side effects (less than 1 person in 10000)

- Stomach pain or diarrhoea but this will usually improve when the dose is reduced
- Feeling sick or actually being sick or suffering from wind

If any of the above become serious or last more than a few days or if you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. How to store MOVICOL Chocolate

Keep out of the reach and sight of children.

Do not use MOVICOL Chocolate after the expiry date shown on the sachet.

Do not store sachet above 25°C.

Once you have made up MOVICOL Chocolate in water, if you cannot drink it straight away keep it covered and in the fridge (2 – 8°C). Throw away any solution not used within a 6 hour period.

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

6. Further information

Each 13.9g sachet of MOVICOL Chocolate contains the following:

Macrogol 3350	13.125 g
Sodium Chloride	0.3507 g
Sodium Hydrogen Carbonate	0.1785 g
Potassium Chloride	0.0317 g

MOVICOL Chocolate also contains chocolate flavour, and acesulfame potassium as a sweetener.

Chocolate flavour contains the following ingredients:

maltodextrin (potato); gum arabic/acacia gum E414, vegetable oils and fats (palm/coconut oil), propylene glycol E1520 and ethyl alcohol.

When it is made into a drink with 125 millilitres of water each sachet gives the equivalent of:

Sodium	65 millimoles/litre
Chloride	51 millimoles/litre
Potassium	5.4 millimoles/litre
Hydrogen Carbonate	17 millimoles/litre

What MOVICOL Chocolate looks like and the contents of the pack

MOVICOL Chocolate is a white to light brown powder.

MOVICOL Chocolate is available in boxes of 20 or 30 sachets.

Marketing authorisation holder:

Norgine Ltd., Moorhall Road, Harefield, Middlesex, UB9 6NS, UK.

Manufacturer:

Norgine Ltd, New Road, Hengoed, Mid Glamorgan, CF82 8SJ, U.K.

MOVICOL Chocolate is available in Europe. In Ireland and Finland it is known as MOVICOL Chocolate, in Austria MOVICOL schoko, in Belgium MOVICOL Chocoladesmaak/MOVICOL Gout chocolat/MOVICOL Schokoladengeschmack and in Sweden MOVICOL Choklad.

Date revised: April 2008

PL 00322/0086



Module 4 Labelling

Line	1-11-11-11-11-11
Print No.	111111
Code No.	17-3-01/0
Size (mm)	145x130x10
Market	UK
Colour 1	Magenta
Colour 2	
Colour 3	Black
Colour 4	N/A
Colour 5	N/A
Pharmacoed	358



*13.9g sachet, powder
for oral solution*

MOVICOL[®]
Chocolate

MOVICOL[®]
Chocolate
*13.9g sachet, powder
for oral solution*

*For the treatment
of constipation*

30 sachets



Each sachet contains:

Mannitol 3350	13.125 g
Sodium chloride	0.3527 g
Sodium hydrogen carbonate	0.1785 g
Potassium chloride	0.0317 g

**On reconstitution in 125ml,
each sachet provides:**

sodium chloride	65 mmol/l
hydrogen carbonate	33 mmol/l
potassium	17 mmol/l
protopium	8.4 mmol/l

Keep all medicines out of the reach and sight of children.
Do not store the sachet above 25°C
Store the reconstituted solution at 2-8°C
(in a refrigerator and keep covered).



MOVICOL[®]
Chocolate
*13.9g sachet, powder
for oral solution*

*For the treatment
of constipation*

30 sachets



Dosage:
Constipation:
Adults, Adolescents and Elderly:
1 - 3 sachets per day according to individual response.
Extended Use: 1 - 2 sachets per day

Faecal Impaction:
8 sachets a day. All should be consumed within a 6 hour period.
Children (Below 12 years of age): not recommended.

For oral use:
Dissolve the contents of one sachet in 125 ml of water then drink it. For faecal impaction it may be easier to dissolve 8 sachets in 1 litre of water.
See Pack leaflet.

Braille Must not move from position indicated

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

On 4th August 2008, Austria, Belgium, Finland, Ireland, and Sweden granted Norgine Limited a Marketing Authorisation (licence) for the medicinal product Movicol Chocolate 13.9g sachet, powder for oral solution (PL 00322/0086; UK/H/0131/004/DC). This application was made by the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a national licence was granted in the UK on 21st August 2008.

The application was made under Article 8.3 of Directive 2001/83/EC, as amended, for a line-extension to the existing product Movicol 13.8g sachet, powder for oral solution (PL 00322/0070; UK/H/0131/001/MR).

This medicine is available through pharmacies and to be promoted to healthcare professionals only (P). It is indicated for the treatment of chronic constipation in adults and children above the age of 12. Movicol Chocolate is also effective in resolving faecal impaction, defined as refractory constipation with faecal loading of the rectum and/or colon.

Movicol Chocolate contains the same active constituents namely macrogol 3350, sodium hydrogen carbonate, sodium chloride and potassium chloride, as Movicol 13.8g (UK PL 00322/0070, UK/H/0131/01). It is not considered that the difference in the flavouring will have any effect on the mechanism of the actives or the efficacy of the drug product.

No new preclinical or clinical studies were conducted, which is acceptable given that the application is a line-extension of an already granted medicinal product.

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.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Movicol Chocolate 13.9g sachet, powder for oral solution
Name(s) of the active substance(s) (INN)	Macrogol 3350, sodium hydrogen carbonate, sodium chloride and potassium chloride
Pharmacotherapeutic classification (ATC code)	Osmotically active laxatives (A06A D65)
Pharmaceutical form and strength(s)	Powder for oral solution containing 13.125g macrogol 3350, 0.3507g sodium chloride, 0.1785g sodium hydrogen carbonate and 0.0317g potassium chloride
Reference numbers for the Decentralised Procedure	UK/H/0131/004/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Finland, Ireland, and Sweden
Marketing Authorisation Number(s)	PL 00322/0086
Name and address of the authorisation holder	Norgine Limited, Chaplin House, Widewater Place, Moorhall Road, Harefield, UB9 6NS

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

Macrogol 3350

INN/Ph.Eur name: Macrogol 3350

Chemical name: N-(2-diethylaminoethyl)-1-benzothiophene-2-carboxamide

Molecular formula: $H-(OCH_2-CH_2)_n-OH$, where n represents the average number of oxyethylene groups (N=3350)

Molecular weight: 276.3971

Macrogol 3350 is the subject of a European Pharmacopoeia monograph.

The manufacture and quality of Macrogol 3350 from all active substance manufacturers are controlled by Certificates of Suitability. Suitable specifications have been provided for all packaging and the primary packaging has been shown to comply with current guidelines concerning contact with food. An appropriate retest period has been determined based on the stability data provided.

Sodium Chloride, Potassium Chloride and Sodium Hydrogen Carbonate

Sodium chloride, potassium chloride and sodium hydrogen carbonate are all subjects of European Pharmacopoeia monographs.

For all other active substances (potassium chloride, sodium chloride and sodium hydrogen carbonate), synthesis of the active substances from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate specifications are provided for sodium chloride, potassium chloride and sodium hydrogen carbonate, 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 and comply with the proposed specification. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Suitable specifications have been provided for all packaging and the primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. A suitable retest period has been set based on this data.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients acesulfame potassium (E950) and chocolate flavour (contains maltodextrin, acacia gum E414, vegetable oils and fats, propylene glycol E1520, and ethyl alcohol).

Acesulfame potassium (E950) is controlled to its European Pharmacopoeia monograph and chocolate flavour is controlled to a suitable in-house specification.

None of the excipients contains materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the pharmaceutical development programme was to produce a product that contained the same levels of active as Movicol 13.8g sachet, powder for oral solution (PL 00322/0070; UK/H/0131/001/MR), but with a chocolate flavour.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the finished product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System

The finished product is packaged in laminate sachets, consisting of four layers (low-density polyethylene, aluminium, low-density polyethylene and paper). These are packaged in boxes in pack sizes of 20 and 30 sachets. The marketing authorisation holder has committed to submitting all packaging to the relevant regulatory authorities for approval before marketing any new pack of product.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current regulations regarding materials for use in contact with food.

Stability of the product

Stability studies were performed on batches of all strengths of finished product and in the packaging proposed for marketing, in accordance with current guidelines. All results from stability studies were within specified limits. These data support a shelf-life of 3 years (6 hours for the reconstituted solution) with the storage instructions “Do not store above 25°C” for the sachet and “Store at 2-8°C (in a refrigerator and keep covered)” for the reconstituted solution.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

The applicant has submitted results of PIL user testing. The results indicate that the PIL 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.

A commitment has been made by the marketing authorisation holder to submit any pack mock-ups to the relevant regulatory authorities for approval before marketing any pack size.

MAA forms

The MAA form is pharmaceutically satisfactory.

Expert report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

The grant of a marketing authorisation is recommended.

III.2 PRE-CLINICAL ASPECTS

1. INTRODUCTION

The expert statement is reproduced in full below:

Movicol (UK PL 00322/0070, UK/H/0131/01) has been licensed in the UK since 18 December 1995 for the treatment of chronic constipation. Subsequently Type II mutual recognition variations were approved for the treatment of faecal impaction and maintenance and long term use in adults, adolescents and the elderly.

Clinical and non-clinical data have previously been submitted and approved to support these indications. There have been no changes to this data.

Movicol Chocolate has the same pharmaceutical form and the same therapeutic indications (chronic constipation and faecal impaction in adults, adolescents and the elderly) as Movicol 13.8g.

Movicol Chocolate contains the same active constituents namely macrogol 3350, sodium hydrogen carbonate, sodium chloride and potassium chloride, as Movicol 13.8g (UK PL 00322/0070, UK/H/0131/01). It is not considered that the difference in the flavouring will have any effect on the mechanism of the actives or the efficacy of the drug product.

Therefore, this application cross-references the non-clinical data submitted for Movicol 13.8g sachet powder for oral solution (UK PL 00322/0070, UK/H/0131/01) and these have not been resubmitted with this application.

All the drug substances in the formulation are well established pharmacopoeial products with good safety profiles. The summary of product characteristics adequately addresses any concerns over toxicity.

As Movicol is well-established and has a good safety profile, there are no concerns over the safety or efficacy of this line-extension marketing authorisation application.

Assessor's comment

Although Norgine has not provided any additional efficacy or safety data to support the above statement, it is accepted that there is no reason to assume that the properties of the new formulation will differ appreciably from those of the currently licensed product.

2. EXCIPIENTS

The excipients are acesulfame potassium Ph Eur (a sweetener) and chocolate flavour. The former is at a higher concentration than in the currently-licensed product. A reformulation of the flavour and sweetener combination was undertaken in order to achieve a drug product with a palatable taste. Acesulfame potassium contributes potassium ions to the reconstituted solution. Potassium ions are one of the declared electrolytes. As a result, adjustments to the acesulfame potassium resulted in a further adjustment to the potassium chloride in the formulation, in order to maintain the declared potassium level. The net effect of this was a reduction of 4% to the chloride ion with negligible effect on the overall formulation.

The latter is International Flavours and Fragrances (IFF) 15.02.9473 and is composed of food-safe ingredients. It is controlled to an in-house specification.

Assessor's comment

Although the Expert Statement does not address the increase in the concentration of acesulfame potassium and the change in the potassium content, it is accepted that there is unlikely to be any change in the toxicity of the product as a result of these adjustments. The Scientific Committee on Food of the European Commission Health and Consumer Protection Directorate-General has concluded that an acceptable daily intake of acesulfame potassium is 0-9 mg/kg/day, which makes the levels of intake from Movicol Chocolate acceptable for a 50 kg adult.

3. IMPURITIES

All of the ingredients are compliant with their European Pharmacopoeia monograph, except for the chocolate flavour. It is accepted that there are no issues regarding impurities.

4. ENVIRONMENTAL RISK ASSESSMENT

There is no requirement for an environmental risk assessment of three of the active ingredients (potassium chloride, sodium chloride and sodium hydrogen carbonate) as they are electrolytes.

An environmental risk assessment for Macrogo1 3350 was provided. The conclusions from the assessment were:

- The $PEC_{SURFACEWATER}$ is estimated to be 525 $\mu\text{g/L}$, which exceeds the 0.01 $\mu\text{g/L}$ action limit that triggers the Phase II assessment.
- The above predicted surface water concentration for Macrogo1 3350 does not take into account biodegradation in the sewage treatment plant. Based on the results of a ready biodegradability test, Macrogo1 3350 is classified as 'readily biodegradable' and as such would be rapidly degraded in the environment.
- Macrogo1 3350 is not likely to reach surface waters as it will be removed by the sewage treatment plant. Continuous exposure to the aquatic environment is not expected therefore; there is no chronic/long term risk to the aquatic ecosystem. The available acute ecotoxicity data that are available for Macrogo1 3350 indicate that it is not toxic to fish and aquatic invertebrates. The fish LC_{50} value was 87,209 mg/L and the daphnia EC_{50} value was 53,484 mg/L.
- No precautionary measures are considered necessary regarding environmental release following the use of Macrogo1 3350 in patients.

The environmental risk assessment was signed by an appropriately qualified person.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The preclinical sections of the SPC are identical to those of similar granted products. The SPC is satisfactory from a preclinical viewpoint.

6. NON-CLINICAL EXPERT REPORT

The non-clinical expert report has been written by an appropriately qualified person.

7. ASSESSOR'S OVERALL CONCLUSION ON THE NON-CLINICAL PART

The applicant has provided an expert statement to support the application for a new, differently-flavoured formulation of Movicol. While the statement is somewhat brief, it is accepted that the change to the chocolate flavour is unlikely to result in any changes in the pharmacodynamic or toxicological properties of Movicol.

There are no objections to the grant of a licence from a non-clinical point of view.

III.3 CLINICAL ASPECTS

Clinical Pharmacology

The clinical pharmacology of the new chocolate-flavoured Movicol is not expected to be different from that of the lemon-flavoured Movicol, as the active ingredients are the same except for the content in potassium chloride, which translates in a reduction of 2mmol/L in the reconstituted solution.

Pharmacokinetics

Macrogol 3350 is unchanged along the gut. It is virtually unabsorbed from the gastrointestinal tract. Any macrogol 3350 that is absorbed is excreted via the urine.

Pharmacodynamics

Macrogol 3350 acts by virtue of its osmotic action in the gut, which induces a laxative effect. Macrogol 3350 increases the stool volume, which triggers colon motility via neuromuscular pathways. The physiological consequence is an improved propulsive colonic transportation of the softened stools and a facilitation of the defecation. Electrolytes combined with macrogol 3350 are exchanged across the intestinal barrier (mucosa) with serum electrolytes and excreted in faecal water without net gain or loss of sodium, potassium and water.

Efficacy

Movicol Chocolate is presented in 13.9g sachets to be made into a solution with 125ml of water before being consumed. In order to have a palatable taste with the new chocolate flavour, the concentration of sweetener had to be increased. The sweetener is acesulfame potassium which, therefore, contributes potassium ions to the reconstituted solution.

The potassium chloride content of the sachets was, therefore, reduced. This is a reduction of 4% for the chloride ion, i.e. a concentration of 51 mmol/L in the reconstituted solution instead of the 53 mmol/L with the original Movicol.

Macrogol plus electrolytes exerts a pharmacological activity by actively securing the net water and electrolyte balance. The combination of macrogol (also known as PolyEthylene Glycol, PEG) and electrolytes amplifies the osmotic gradient and prevents undue net electrolyte loss or gain. Water and electrolytes ingested with the product are absorbed from the proximal gastrointestinal tract. Due to the osmotic activity of macrogol, an equivalent amount of water and electrolytes is then secreted into the distal gastrointestinal tract and excreted in the faeces. While one balance no net gain or loss of electrolytes and water occurs, the electrolyte components of the products and the secreted electrolytes are transported across

biological membranes. This direct impact on systemic water and electrolyte homeostasis clearly shows that the actions of macrogol plus electrolytes by large exceed those of a merely intra-luminal hydration of the stool.

Hence, the variation in chloride ion content, considering that the Reference Nutrient Intake for chloride is 2,500mg/day, is considered to be of no clinical significance.

However the higher content in acesulfame potassium has not been discussed, nor was the risk of bitter aftertaste that is a well-known fact with this sweetener.

In conclusion, the efficacy of the chocolate-flavoured Movicol is expected to be same as that of the regular lemon-flavoured Movicol.

Safety

The excipients are acesulfame potassium Ph Eur and chocolate flavour. The latter is International Flavours and Fragrances (IFF) 15.02.9473 and is composed of food-safe ingredients. It is controlled to an in-house specification.

No safety issue is expected with the changes in the formulation from that of Movicol.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels

The SPC, PIL and Labels are medically acceptable and consistent with those for previously granted Movicol products, where appropriate.

Conclusion

The grant of a marketing authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of Movicol Chocolate 13.9 sachet, powder for oral solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type. The applicant has provided an expert statement to support the application for a new, differently-flavoured formulation of Movicol. While the statement is somewhat brief, it is accepted that the change to the chocolate flavour is unlikely to result in any changes in the pharmacodynamic or toxicological properties of Movicol.

EFFICACY

The efficacy of this product is identical to that of Movicol 13.8g sachet, powder for oral solution (PL 00322/0070; UK/H/0131/001/MR), albeit with a reduction of 4% for the chloride ion content (due to a reduction in potassium chloride). This reduction is not considered to be of clinical significance and the efficacy of chocolate-flavoured Movicol is expected to be same as that of the regular lemon-flavoured Movicol.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Movicol 13.8g sachet, powder for oral solution (PL 00322/0070; UK/H/0131/001/MR).

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with the active substances in similar formulations is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome