Public Assessment Report

Decentralised Procedure

MOVICOL Liquid Orange flavour, concentrate for oral solution

Macrogol 3350
Sodium chloride
Sodium hydrogen carbonate
Potassium chloride

PL 20011/0007

UK/H/0131/06/DC

Norgine Pharmaceuticals Limited
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Norgine Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product MOVICOL Liquid Orange flavour, concentrate for oral solution (product licence number: PL 20011/0007) on 25 May 2011. This medicine can be bought from pharmacies without a prescription.

MOVICOL concentrate for oral solution is used to treat chronic constipation.

The data submitted in support of this application for MOVICOL concentrate for oral solution raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
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### Module 1

**Information about Decentralised Procedure**

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>MOVICOL Liquid Orange flavour, concentrate for oral solution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of application</strong></td>
<td>Article 8.3 (known active substance)</td>
</tr>
<tr>
<td><strong>Name of the active substance (INN)</strong></td>
<td>Macrogol 3350, sodium chloride, sodium hydrogen carbonate, potassium chloride</td>
</tr>
<tr>
<td><strong>Pharmacotherapeutic classification (ATC code)</strong></td>
<td>Osmotically acting laxatives (A06A D65)</td>
</tr>
<tr>
<td><strong>Pharmaceutical form and strength</strong></td>
<td>Concentrate for oral solution, Macrogol 3350: 13.125 g Sodium chloride: 0.3507 g Sodium hydrogen carbonate: 0.1785 g Potassium chloride: 0.0466 g</td>
</tr>
<tr>
<td><strong>Reference number for the Decentralised Procedure</strong></td>
<td>UK/H/0131/06/DC</td>
</tr>
<tr>
<td><strong>Reference Member State</strong></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>Member States concerned</strong></td>
<td>AT, BE, DE, ES, FI, IE, IT, PT, SE</td>
</tr>
<tr>
<td><strong>Start of Decentralised Procedure</strong></td>
<td>6 January 2010</td>
</tr>
<tr>
<td><strong>End date of Decentralised Procedure</strong></td>
<td>10 March 2011</td>
</tr>
<tr>
<td><strong>Marketing Authorisation number</strong></td>
<td>PL 20011/0007</td>
</tr>
<tr>
<td><strong>Name and address of the authorisation holder</strong></td>
<td>Norgine Pharmaceuticals Limited Norgine House Widewater Place Harefield Uxbridge UB9 6NS United Kingdom</td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
MOVICOL Liquid Orange flavour, concentrate for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 25 ml of MOVICOL Liquid Orange flavour contains the following active ingredients:
- Macrogol 3350: 13.125 g
- Sodium chloride: 0.3507 g
- Sodium hydrogen carbonate: 0.1785 g
- Potassium chloride: 0.0466 g

The concentration of electrolyte ions present when a 25 ml dose is made up to 125 ml of solution is as follows:
- Sodium: 65 mmol/l
- Chloride: 53 mmol/l
- Potassium: 5.4 mmol/l
- Hydrogen carbonate: 17 mmol/l

This corresponds to the following amount of each electrolyte in each diluted dose of 125 ml:
- Sodium: 8.125 mmol
- Chloride: 6.625 mmol
- Potassium: 0.675 mmol
- Hydrogen carbonate: 2.125 mmol

Excipients:
- 74.5 mg ethyl alcohol per 25 ml
- 11.3 mg methyl parahydroxybenzoate (E218) per 25 ml
- 5.6 mg ethyl parahydroxybenzoate (E214) per 25 ml

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for oral solution.
Clear, colourless liquid

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
For the treatment of chronic constipation.
4.2 **Posology and method of administration**
A course of treatment for constipation with MOVICOL Liquid Orange flavour does not normally exceed 2 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 the elderly:** 25 ml diluted in 100 ml of water 1-3 times daily in divided doses, according to individual response. For extended use, the dose can be adjusted down to 1 or 2 doses per day of 25 ml diluted in 100 ml of water.

**Children:** MOVICOL Liquid Orange flavour is not recommended for use in children below the age of 12 years. Alternative MOVICOL products are available for children.

**Patients with renal insufficiency:** No dosage change is necessary for the treatment of constipation.

**Faecal Impaction:** MOVICOL Liquid Orange flavour is not recommended for use for the treatment of faecal impaction (see section 4.4). Alternative MOVICOL products are available for the treatment of faecal impaction.

**Administration**
The product must not be taken undiluted and may only be diluted in water. For instructions on dilution of the product before administration, see section 6.6.

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 substances or to any of the excipients.

4.4 **Special warnings and precautions for use**
Mild adverse drug reactions are possible as indicated in Section 4.8. If patients develop any symptoms indicating shifts of fluids/electrolytes (e.g. oedema, shortness of breath, increasing fatigue, dehydration, cardiac failure) MOVICOL Liquid Orange flavour should be stopped immediately and electrolytes measured and any abnormality should be treated appropriately.

The absorption of other medicinal products could transiently be reduced due to an increase in gastro-intestinal transit rate induced by MOVICOL Liquid Orange flavour (see section 4.5).

This medicinal product contains 8.125 mmol of sodium in each diluted dose of 125 ml. The sodium content of MOVICOL Liquid Orange flavour should be
taken into consideration when administering the product to patients on a controlled sodium diet.

This medicinal product contains 45.6 mg of benzyl alcohol in each diluted dose of 125 ml. The maximum recommended daily dose (MRD)(25ml diluted in 100ml of water taken three times a day) contains 136.8mg of benzyl alcohol. The Acceptable Daily Intake (ADI) of benzyl alcohol is 5 mg/kg body weight. The maximum daily dose (25 ml diluted in 100 ml of water 1-3 times daily) should not be exceeded.

This product contains ethyl (E214) and methyl (E218) parahydroxybenzoates which may cause allergic reactions, possibly delayed.

4.5 Interaction with other medicinal products and other forms of interaction
Macrogol raises the solubility of medicinal products that are soluble in alcohol and relatively insoluble in water.
There is a possibility that the absorption of other medicinal products could be transiently reduced during use with MOVICOL Liquid Orange flavour (see section 4.4). There have been isolated reports of decreased efficacy with some concomitantly administered medicinal products, e.g. anti-epileptics.

4.6 Pregnancy and lactation

Pregnancy
There is no experience of the use of MOVICOL Liquid Orange flavour during pregnancy. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). MOVICOL Liquid Orange flavour should not be used during pregnancy unless clearly necessary.

Lactation
It is unknown whether MOVICOL Liquid Orange flavour is excreted in human milk.
A risk to the suckling child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from MOVICOL Liquid Orange flavour therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on the effects of MOVICOL on fertility.

4.7 Effects on ability to drive and use machines
MOVICOL Liquid Orange flavour has no influence on the ability to drive and use machines.

4.8 Undesirable effects
Reactions related to the gastrointestinal tract occur most commonly.

These reactions may occur as a consequence of expansion of the contents of the gastrointestinal tract, and an increase in motility due to the pharmacologic
effects of MOVICOL Liquid Orange flavour. Mild diarrhoea usually responds to dose reduction.

The frequency of the adverse events is not known as it cannot be estimated from the available data.

<table>
<thead>
<tr>
<th>System Order Class</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Allergic reactions, including anaphylaxis, angioedema, dyspnoea, rash, erythema, urticaria, and pruritis.</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Electrolyte disturbances, particularly hyperkalaemia and hypokalaemia.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, diarrhoea, vomiting, nausea, dyspepsia, abdominal distension, borborygmi, flatulence, anal discomfort.</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Peripheral oedema</td>
</tr>
</tbody>
</table>

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

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.

Clinical studies in the use of MOVICOL sachets (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 of powdered MOVICOL a day (one sachet is equivalent to 25 ml of MOVICOL Liquid Orange flavour), 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 weight macrogols that provide evidence of safety at the recommended therapeutic dose.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
- Acesulfame potassium E950
- Sucralose E955
- Benzyl alcohol
- Methyl parahydroxybenzoate E218
- Ethyl parahydroxybenzoate E214
- Orange flavour (contains flavouring substances, flavouring preparations and ethanol)
- Purified water

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
- Unopened: 2 years
-Opened: 30 days
-Diluted solution shelf-life: 24 hours

6.4 **Special precautions for storage**
- Bottle: Do not refrigerate or freeze.
- Diluted solution: Keep solution covered.

6.5 **Nature and contents of container**
Polyethylene terephthalate bottle with polypropylene – low density polyethylene child-resistant closure with polyethylene liner.
Each carton contains one bottle and a polypropylene measuring cup.

Pack size: 500ml bottle

6.6 **Special precautions for disposal**
The product should be diluted as follows:
25 ml should be measured out using the dosing cup provided or five 5 ml teaspoonfuls. This should be diluted in 100 ml (approximately half a glass) of water.

Any unused solution should be discarded within 24 hours.
7 MARKETING AUTHORISATION HOLDER
Norgine Pharmaceuticals Limited
Norgine House
Widewater Place
Harefield
Uxbridge
UB9 6NS

8 MARKETING AUTHORISATION NUMBER(S)
PL 20011/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/05/2011

10 DATE OF REVISION OF THE TEXT
25/05/2011
Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

MOVICOL®
Liquid Orange flavour
Concentrate for oral solution
For a list of active substances, please see section 6.

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription. However, you still need to take MOVICOL Liquid Orange flavour 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 should contact a doctor if your symptoms worsen or do not improve.
- If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

If you need the information on this leaflet in an alternative format, such as large text, or braille, please ring from the UK 0800 198 5000.

In this leaflet:
1. What MOVICOL Liquid Orange flavour is and what it is used for
2. Before you take MOVICOL Liquid Orange flavour
3. How to take MOVICOL Liquid Orange flavour
4. Possible side effects
5. How to store MOVICOL Liquid Orange flavour
6. Further information

1. WHAT MOVICOL LIQUID ORANGE FLAVOUR IS AND WHAT IT IS USED FOR

The name of this medicine is MOVICOL Liquid Orange flavour concentrate for oral solution.

It is a laxative for the treatment of chronic constipation in adults, adolescents, and elderly. It is not recommended for children below 12 years of age.

MOVICOL Liquid Orange flavour helps you to achieve a comfortable bowel movement even if you have been constipated for a long time.

You must not use MOVICOL Liquid Orange flavour if you have a very bad constipation called faecal impaction.

2. BEFORE YOU TAKE MOVICOL LIQUID ORANGE FLAVOUR

Do not take MOVICOL Liquid Orange flavour if your doctor has told you that you:
- have a blockage in your intestine (gut obstruction, ileus)
- have a perforated gut wall
- have a severe inflammatory bowel disease like ulcerative colitis
- have Crohn's disease or toxic megacolon
- are allergic (hypersensitive) to the active substances or any of the other ingredients of MOVICOL Liquid Orange flavour.

3. HOW TO TAKE MOVICOL LIQUID ORANGE FLAVOUR

This product must be diluted before use.

A dose of MOVICOL Liquid Orange Flavour is 25 ml liquid diluted in 100 ml of water. Take this 1–3 times a day according to the severity of your constipation.

How to mix:
Open the bottle and measure 25 ml or five 5 ml teaspoonfuls.
Pour the liquid into a glass and then add 100 ml (about half a glassful of water). Stir well until all the liquid has been evenly mixed and the diluted MOVICOL Liquid Orange Flavour solution is clear, then drink it.

Pour the mixture into the water. If necessary, the dose may be reduced to either 1 or 2 doses a day.

Taking other medicines

Some medicines, e.g. antiepileptics, (medicines for epilepsy) may not work as effectively during use with MOVICOL Liquid Orange flavour. Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription.

Taking MOVICOL Liquid Orange Flavour with food and drink

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

Pregnancy and breast-feeding

If you are pregnant or breast-feeding talk to your doctor before taking MOVICOL Liquid Orange Flavour.

Driving and using machines

MOVICOL Liquid Orange Flavour does not affect your ability to drive or use machines.

Important information about some of the ingredients of MOVICOL Liquid Orange Flavour

This medicinal product contains ethyl and methyl parahydroxybenzoate which may cause allergic reactions, possibly delayed.

It also contains:
- small amounts of ethanol (alcohol), less than 100 mg per 25 ml dose
- 45.6 mg of benzo alcohol in each diluted dose of 125 ml.
Do not exceed the stated dose.

4. POSSIBLE SIDE EFFECTS

Some people may experience:
- a feeling of having to go to the toilet
- a change in the way they pass their stools

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

5. HOW TO STORE MOVICOL LIQUID ORANGE FLAVOUR

Keep out of the reach and sight of children.

Store in a cool place, below 25°C (77°F), in an airtight container.

6. ADDITIONAL INFORMATION

If you think you have taken too much of this medicine, tell your doctor or pharmacist straight away.

What to do if you forget to take the medicine

Take as soon as you remember unless it is almost time for your next dose.

What to do if you stop taking the medicine

Continue to take MOVICOL Liquid Orange Flavour as directed until you have no more symptoms.

How to dispose of remaining medicine

Do not flush medicines down the toilet or pour them down a sink. Please take back to a pharmacy or your doctor's surgery.

7. FURTHER INFORMATION

If you are not sure about any of the information given in this leaflet, ask your doctor or pharmacist for advice.

Date of printing: 07/05/2021
If you take more MOVICOL Liquid Orange Flavour than you should
You may develop excessive diarrhoea, which can lead to dehydration. If this occurs, stop taking MOVICOL Liquid Orange Flavour and drink plenty of fluids. If you are worried contact your doctor or pharmacist.

If you forget to take MOVICOL Liquid Orange Flavour
Take the dose as soon as you remember to take it.

4. POSSIBLE SIDE EFFECTS
Like all medicines, MOVICOL Liquid Orange Flavour can cause side effects although not everybody gets them.

If you have a severe allergic reaction which causes difficulty in breathing, or swelling of the face, lips, tongue or throat, tell your doctor immediately and stop taking MOVICOL Liquid Orange Flavour.

Other allergic reactions may occur which may cause a skin rash, reddening of the skin or a nettle rash, swollen hands, feet or ankles and headache.

Other side effects may also include indigestion, stomach ache or nausea and tired and low levels of potassium in the blood. You may also feel bloated, suffer from wind, feel sick or vomit, may also experience screens of the anus (bottom) and may have mild diarrhoea when starting to take MOVICOL Liquid Orange Flavour which generally gets better if you reduce the amount of MOVICOL Liquid Orange Flavour you take.

If any of the side effects gets serious or lasts more than a few days or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE MOVICOL LIQUID ORANGE FLAVOUR
Keep out of the reach and sight of children.

Do not use MOVICOL Liquid Orange Flavour after the expiry date which is stated on the bottle. The expiry date refers to the last day of that month.

Do not refrigerate or freeze.

Discard any remaining product 30 days after first opening the bottle.

Once you have diluted MOVICOL Liquid Orange Flavour in water, if you cannot drink it straight away keep it covered. Throw away any solution not used within a 24 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
What MOVICOL Liquid Orange Flavour contains
Each 25 ml of MOVICOL Liquid Orange Flavour contains the following:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrogol 3350</td>
<td>13.125 g</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>0.3507 g</td>
</tr>
<tr>
<td>Sodium Hydrogen Carbonate</td>
<td>0.1785 g</td>
</tr>
<tr>
<td>Potassium Chloride</td>
<td>0.0466 g</td>
</tr>
</tbody>
</table>

MOVICOL Liquid Orange Flavour also contains purified water, orange flavour, and acesulfame potassium (E950) and sucrose (E955) as sweeteners. It also contains a preservative which contains benzyl alcohol, methyl parahydroxybenzoate (E219) and ethyl parahydroxybenzoate (E218).

Orange flavour contains the following ingredients: flavouring substances, flavouring preparations and ethanol (alcohol).

When each 25 ml is made into a drink with 100 millilitres of water, it gives the equivalent of:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>0.5 millimoles/ltre</td>
</tr>
<tr>
<td>Chloride</td>
<td>0.5 millimoles/ltre</td>
</tr>
<tr>
<td>Potassium</td>
<td>5.4 millimoles/ltre</td>
</tr>
<tr>
<td>Carbonate Hydrogen</td>
<td>17 millimoles/ltre</td>
</tr>
</tbody>
</table>

MOVICOL Liquid Orange Flavour contains 8.125 mmol of sodium in each diluted dose of 125 ml. To be taken into consideration by patients on a controlled sodium diet.

What MOVICOL Liquid Orange Flavour looks like and contents of the pack
Each pack consists of a carton with a plastic bottle of MOVICOL Liquid Orange Flavour containing 500 ml of solution and a plastic dosing cup.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation Holder is Norgine Pharmaceuticals Ltd, Wildeywater Place, Moonhall Rd, Halefield, Middlesex, UB9 6NS, UK.

The Manufacturer is Norgine Pharma Dreux, 29, Rue Ethé Vertin, 28109 Dreux Cedex, France.

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

- Austria: MOVICOL Liquid Orangengeschmack
- Belgium: MOVICOL Vloeibaar Sinaasappelsmaak
- Germany: MOVICOL Flüssig Orangengeschmack
- Finland: MOVICOL Liquido Orange
- Ireland: MOVICOL Liquid Orange Flavour
- Italy: MOVICOL Concentrato per soluzione orale, gusto Arancia
- Portugal: MOVICOL Laranja Solução
- Spain: MOVICOL Sabor naranja Solución
- Sweden: MOVICOL Lösning Apelsin
- United Kingdom: MOVICOL Liquid Orange Flavour

This leaflet was last approved in March 2011
Module 4

Labelling

Label:

Each 25 ml of MOVICOL Liquid Orange flavour contains:
- Macrogol 3350: 13.125 g
- Sodium chloride: 0.3507 g
- Sodium hydrogen carbonate: 0.1785 g
- Potassium chloride: 0.0466 g
- Also contains ethanol (alcohol), E214, E218.

See leaflet for further information.

For the treatment of chronic constipation.
Not recommended for the treatment of faecal impaction.

DOSAGE:

This product must be diluted before use.
Adults, adolescents and elderly: 1-3 doses per day of 25ml of MOVICOL Liquid Orange flavour diluted in 100ml of water, according to individual response.

Do not exceed the maximum daily dose.
Children (below 12 years of age): not recommended.

Do not refrigerate or freeze. Discard product 30 days after first opening.
Read the package leaflet before use.
Keep out of the reach and sight of children.

Norgine Pharmaceuticals Limited,
Widewater Place, Moorhall Road,
Harefield, Middlesex, UB9 6NS UK
PL 20011/0007
Module 5
Scientific Discussion

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the application for MOVICOL Liquid Orange flavour, concentrate for oral solution in the treatment of chronic constipation could be approved.

EXECUTIVE SUMMARY

Problem statement
This application was submitted according to Article 8.3 of Directive 2001/83/EC, for a new product with a known active substance (with the addition of a new strength and a new pharmaceutical form). The application is a line extension to the Marketing Authorisation for Movicol 13.8 g sachet, powder for oral solution, which was granted in the UK on 9 January 1996 (PL 00322/0070) and was also approved in AT, BE, DE, ES, FI, IE, IT, PT and SE through Mutual Recognition Procedure UK/H/0131/001.

With the UK acting as RMS in this Decentralised Procedure (DCP), Norgine Pharmaceuticals Limited sought Marketing Authorisation for MOVICOL concentrate for oral solution in Austria, Belgium, Germany, Spain, Finland, Ireland, Italy, Portugal and Sweden.

About the product
This application represents a change in pharmaceutical form and the flavour, sweetener and preservative excipients. The product was developed as a convenient dosage option with a new flavour. The currently marketed Movicol products require reconstitution of powder in water, which can take up to three minutes. Offering patients a liquid formulation which is quicker to make up would result in improved patient compliance.

Macrogol plus electrolytes exerts pharmacological activity by actively securing the net water and electrolyte balance. The combination of macrogol 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, on 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 exceed those of a merely intra-luminal hydration of the stool.

Movicol powder for oral solution is approved for the treatment of chronic constipation and faecal impaction in adults, adolescents and the elderly. The proposed indication for MOVICOL concentrate for oral solution is chronic constipation in adults, adolescents and the elderly.
General comments on the submitted dossier
The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall summaries of the dossier regarding the quality, preclinical and clinical parts have been submitted.

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

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

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

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of 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.

GLP
No new preclinical studies were submitted with this application. The GLP status of the literature data referenced in the preclinical section of the dossier cannot be verified.

GCP
No new clinical studies were submitted with this application. A bioequivalence study has not been performed.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substances
This product contains the drug substances macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride.

(1) Macrogol 3350

INN: Macrogol 3350
Chemical name: N-(2-diethylaminoethyl)-1-benzothiophene-2-carboxamide
Molecular formula: H-(OCH₂-CH₂)ₙ-OH, where n represents the average number of oxyethylene groups (N=3350)
Molecular weight: 276.3971
CAS number: 25322-68-3
General Properties: White or almost white solid with a waxy or paraffin-like appearance. Very soluble in water and in methylene chloride, very slightly soluble in alcohol, practically insoluble in fatty oils and in mineral oils

(2) Sodium chloride

INN: Sodium chloride
Molecular formula: NaCl
Molecular weight: 58.44
CAS number: 7647-14-5
General Properties: Sodium chloride is a white, crystalline powder or colourless crystals or white pearls, freely soluble in water, practically insoluble in ethanol

(3) Sodium hydrogen carbonate

INN: Sodium hydrogen carbonate
Chemical name: Sodium bicarbonate
Molecular formula: NaHCO₃
Molecular weight: 84.01
CAS number: 144-55-8
General Properties: Sodium hydrogen carbonate is a white or almost white, slightly granular powder, soluble in water, practically insoluble in ethanol

(4) Potassium chloride

INN: Potassium chloride
Molecular formula: KCl
Molecular weight: 74.6
CAS number: 7447-40-7
General Properties: Potassium chloride is a white or almost white crystalline powder or colourless crystals, freely soluble in water, practically insoluble in ethanol

All four drug substances are well-known and comply with the Ph Eur. All aspects of the manufacture and control of macrogol 3350, sodium chloride and sodium hydrogen carbonate are supported by an EDQM Certificate of Suitability. These certificates are accepted as confirmation of the suitability of these drug substances for inclusion in this medicinal product.

All four drug substances are stable materials and appropriate information regarding their stability is included in the application. They have been previously approved for use in Movicol preparations that are mutually recognised in EU member states.

Drug product
The drug product is a clear, colourless liquid containing 13.125 g macrogol 3350, 0.3507 g sodium chloride, 0.1785 g sodium hydrogen carbonate, 0.0466 g potassium chloride and the pharmaceutical excipients acesulfame potassium (E950), sucralose (E955), benzyl alcohol, methyl parahydroxybenzoate (E218), ethyl parahydroxybenzoate (E214), orange flavour (containing flavouring substances, flavouring preparations and ethanol) and purified water.

All the excipients are compendial, with the exception of the orange flavour, which is controlled by a suitable in-house specification; in the absence of a relevant monograph for this excipient, this is acceptable. Satisfactory certificates of analysis have been provided for all excipients. Suitable declarations issued by suppliers of the excipients confirming compliance with the requirements of the relevant guideline and Directives with regard to TSE are provided.

**Pharmaceutical development**
A satisfactory account of the pharmaceutical development of the product has been provided.

**Product manufacture**
A satisfactory account of the manufacturing process has been provided. In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory details of a process validation scheme have been provided.

**Finished product specification**
The finished product specification is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-closure system**
MOVICOL concentrate for oral solution is stored in a 500 ml polyethylene terephthalate bottle with a polypropylene/low density polyethylene child-resistant closure with polyethylene liner. Each carton contains one bottle and a polypropylene measuring cup.
Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for this product when the packaging is unopened. Once the packaging is opened a shelf life of 30 days applies, and the diluted solution has a shelf life of 24 hours. The special precautions for storage are ‘Do not refrigerate or freeze’ and ‘Keep solution covered’ (for diluted solution).

**Product literature**
The SmPC, PIL and labels are pharmaceutically acceptable.
A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), 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.

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

**Quality conclusion**
There are no objections to the approval of MOVICOL concentrate for oral solution from a quality point of view.

**Preclinical aspects**

**Preclinical overview**
The pharmacological, pharmacokinetic and toxicological properties of macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride are well known. As these drug substances are well known, no preclinical studies are required, and the applicant has provided none. An overview based on a literature review is, thus, appropriate.

The preclinical overview was written by an appropriately qualified toxicologist. It lists nine references up to 2009 and is dated the 27 August 2009. This is acceptable.

**Environmental Risk Assessment**
The applicant provided an assessment of the environmental risk for macrogol 3350. The use of this product is not expected to increase the overall use of macrogol 3350. PEC_{surface,water} was 197 µg/L for macrogol 3350, this is above the action limit of 0.01 µg/L. A calculation for logK_{ow} has not been provided, although the applicant has screened for biodegradability, persistence, bioaccumulation and toxicity. The applicant has argued that macrogol 3350 is not likely to reach surface waters as it will be removed by STP and continuous exposure to the aquatic environment is not expected. This is acceptable.

**Product literature**
The product literature is acceptable from a preclinical point of view.

**Preclinical conclusion**
There are no objections to the approval of MOVICOL concentrate for oral solution from a preclinical point of view.
Clinical aspects

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
The pharmacodynamic characteristics of the drug substances have been well-studied in the past. There would be no particular concerns for this medicinal product. No new data have been submitted and none are required.

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.

Clinical efficacy
MOVICOL concentrate for oral solution is not expected to be different to Movicol 13.8 g sachet, powder for oral solution. The product administered when taking MOVICOL concentrate for oral solution is essentially the same as the powder for oral solution; the only difference being that MOVICOL concentrate for oral solution taken by the user is produced by dilution of a concentrated liquid rather than reconstitution from a powder. New efficacy data is, therefore, not needed.

Clinical safety
MOVICOL concentrate for oral solution contains ingredients (orange flavour, purified water, sucralose and benzyl alcohol and hydroxybenzoate preservatives) that are not present in the powder. The level of benzyl alcohol ingested on a daily basis would exceed the ADI if the concentrate product was used for the indication faecal impaction. The applicant has, therefore, proposed to restrict the indication to chronic constipation, which would be different to the indications of the powder. Additional warnings in the SmPC and PIL have been included to reflect this. This is acceptable.

Pharmacovigilance system
The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk Management Plan
The drug substances are well established and there are many years of experience to enable safety monitoring via routine risk minimisation. Therefore, in line with CHMP/96268/2005, no risk management plan has been provided. This is satisfactory.

Periodic Safety Update Report (PSUR)
A PSUR cycle in line with other Movicol products is acceptable.
Expert report
A Clinical Expert Statement written by an appropriately qualified physician (dated 3 September 2009) is provided. This is satisfactory.

Product literature
All product literature (SmPC, PIL and labelling) are medically satisfactory.

Clinical conclusion
There are no objections to the approval of MOVICOL concentrate for oral solution from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of MOVICOL concentrate 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 these type.

EFFICACY
The use of the drug substances in the treatment of chronic constipation is well established. New efficacy data is, therefore, not needed.

SAFETY
No new or unexpected safety concerns arise from this application.

The SmPCs and PIL are satisfactory and consistent with those for Movicol 13.8 g sachet, powder for oral solution. Satisfactory labelling has also been submitted.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with the drug substances is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk ratio is, therefore, considered to be acceptable. A Marketing Authorisation should be granted.