LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Movicol Junior Neutral
(macrogol, potassium chloride, sodium chloride, sodium hydrogen carbonate)

SE/H/1799/03/E/01

This module reflects the scientific discussion for the approval of Movicol Junior Neutral. The procedure was finalised on 2021-12-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Movicol Junior Neutral, powder for oral solution in sachet.

The active substances are macrogol, potassium chloride, sodium chloride, sodium hydrogen carbonate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application is an extension, new strength, of the previously authorised product Movicol, powder for oral solution in sachet (SE/H/1799/01), marketed by Norgine Healthcare B.V. since 1996. Please note that a Public Assessment Report is not available for Movicol.

The a.m. extension application for **Movicol Junior Neutral**, powder for oral solution, in sachet, is submitted according to Article 8(3) (known active substance) of Directive 2001/83/EC. The applicant, Norgine BV, applies for a marketing authorisation in LU, MT and PT through this repeat use procedure with Sweden acting as reference member state (RMS). The product was first approved through an MRP, finalised in 2005, with UK as RMS (UK/H/131/03). The RMS-ship was transferred to Sweden in 2018 (UK/H/131/03 --> SE/H/1799/03) and current CMS are: AT, BE, DE, ES, FI, IE, IT, XI.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

No new non-clinical studies have been conducted for this extension application, which is accepted. No separate non-clinical report was prepared.

Environmental Risk Assessment (ERA)
Since Movicol Junior Neutral is a well-known product and is already existing on the market, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

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

Pharmacokinetics
N/A

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

Clinical efficacy
For the indication that was initially granted, clinical studies in support of the application comprised nine company sponsored trials using Movicol. All have been previously assessed by the relevant authorities within the European Union where the product is approved. These are summarised in Table 1 below.

Table 1. Summary of the clinical trials.

	Study investigator and year	Indication	No. of patients analysed	Previously assessed by the MCA
CT1	Chaussade 1989	Chronic constipation	32 (24 on Movicol)	Yes, original MAA 1995
CT2	Lemann 1995	Chronic constipation	115 (60 on Movicol)	Yes, original MAA 1995
CT3	Alix E 1995	Chronic constipation	28	Yes, original MAA 1995
CT4	Schlosser A 1996	Chronic constipation	40	Yes, approved variation MRP UK/H/131/1/W13
CT5	Habertmann W and Schlosser A 1996	Chronic constipation	2011	Yes, approved variation MRP UK/H/131/1/W13
CT6	Ulm G 2001	Chronic constipation	544	YES, APPROVED VARIATION MRP UK/H/131/1/W13
CT7	Migneon-Duballet 2000	Chronic constipation	54	YES, APPROVED VARIATION MRP UK/H/131/1/W13
CT8	Ferguson A 1997	Faecal impaction (faecaloma)	27	Yes, approved variation MRP UK/H/131/1/W13
CT9	Alix A 199	Faecaloma	11	No, -new study

The data for efficacy for Movicol was based on one pivotal clinical trial involving 60 children (Norgine Protocol 99/05). This was supported by data from a retrospective published study which was conducted at the same centre as the pivotal study (R. Vincent, D. C. A. Candy, 2001). In addition, support of efficacy for the use of Movicol-Paediatric was provided by the use of lavage preparation in various publications submitted with the application. The two studies are summarised below.

Norgine Protocol 99/05

This was a single centre study to assess the safety and efficacy of Movicol in the treatment of faecal impaction in children aged 2-11 years (phase I) followed by a double blind, randomised phase to compare the efficacy and safety of Movicol and Duphalac Dry (lactulose) for maintenance therapy(phase II).

Phase I was up to 7 days open label evaluation of Movicol administered to patients in hospital until disimpaction occurred followed by 2 days of Movicol at the disimpaction dose. Phase II was a 12 week randomised double blind comparison of Movicol and Duphalac as maintenance therapy on an out-patient basis. A total of 65 patients were enrolled into the study and 63 (43 male & 20 female) patients were evaluated.

Only the results of phase I of the study are provided. Disimpaction was achieved in 58 of the 63 patients analysed. Three out of the five children withdrew during the early stages of the study and the remaining two patients failed to disimpact – one child in each age group. The mean time taken to disimpact was 5.7 days as shown in table 2 below.

Table 2: Disimpaction results for the study population

		AGE 2-4 YEARS (N=28)	**AGE 5-11YEARS (N=35)**	**Total (N=63)**
Disimpaction achieved [number (%) patients]	Yes No[1]	25 (89) 3 (11)	33 (94) 2 (6)	58 (92) 5 (8)
Time taken to disimpact (days)	N Mean SD Median Range	25 5.8 1.2 6.0 3-7	33 5.6 1.1 6.0 3-7	58 5.7 1.2 6.0 3-7
Additional intervention [number (%) patients][2]	Yes No	0 (0) 25 (100)	0 (0) 33 (100)	0 (0) 58 (100)
Total Number of doses	N Mean SD Range	25 14.3 4.5 5-19	33 23.6 6.8 9-32	58 19.6 7.5 5-32

1= Three patients withdrew before the end of the study, 2 = Percentages are based on the number of children who achieved disimpaction.

Compliance with study medication was good and greater in the older age group in comparison to the younger group. No intervention of other laxatives was required during the study.

Study by R Vincent, D C A Candy, 2001
This publication retrospective study reports on 30 patients (17M, 13F) with faecal impaction aged between 2-15 years. An escalating dosage regime was employed and Movicol 13.8g was administered until the children were passing watery stools and then adjusted until a soft and regular stool resulted. Disimpaction was achieved in all 30 patients (100%) without the intervention of further laxatives.

In addition, the applicant has provided extensive supportive data with accompanying review and discussion regarding the use of polyethylene glycol and electrolytes bowel lavage solutions for bowel preparation in children. Overall, the studies discussed demonstrate the effectiveness of these preparations as lavage solutions and for treating children with faecal impaction.

Type II variation after approval

In 2020, in the procedure SE/H/1799/03/II/186, a modification of the approved indication chronic constipation for Movicol Junior Neutral, to extend the age range of the current indication of Movicol Junior Neutral to include children from 1 to 2 years of age was approved.

Clinical safety
The incidences of adverse events in the pivotal Norgine protocol 99/05 are provided in Table 3 below.

Table 3. Reported Adverse Events in Norgine Study 99/05

BODY SYSTEM	**Age 2-4 years (N=28) (%)**	**Age 5-11 years (N=35) (%)**	**Total (N=63) (%)**
Overall total	18 (64)	21 (60)	39 (62)
Cardiac disorders	0 (0)	2 (6)	2 (3)
Ear and labyrinth disorders	0 (0)	1 (3)	1 (2)
Eye disorders	0 (0)	1 (3)	1 (2)
Gastrointestinal disorders	15 (54)	11 (31)	26 (41)
General disorders and administration site conditions	8 (29)	1 (3)	9 (14)
Infections and infestations	0 (0)	1 (3)	1 (2)
Injury and poisoning	0 (0)	2 (6)	2 (3)
Investigations	0 (0)	1 (3)	3 (5)
Musculoskeletal, connective tissue and bone disorders	2 (7)	1 (3)	3 (5)
Nervous system disorders	2 (7)	7 (20)	9 (14)
Renal and urinary disorders	0 (0)	1 (3)	1 (2)
Respiratory and thoracic disorders	3 (11)	3 (9)	6 (10)
Skin disorders	1 (4)	1 (3)	2 (3)

In total, 39 children (62%) from the safety population experienced adverse events with 18 from the 2-4 age group and 21 from the 5-11 age group. The most commonly reported events were gastrointestinal disorders experienced by 26 (41%) children.

Most gastrointestinal events were judged by the investigator to be at least possibly related to the study treatment and were mild in severity. Two episodes of abdominal pain were recorded as severe and judged by the investigator to be possibly related to the study medication. All adverse events had resolved by the end of the study. No serious adverse events were observed during the study.

Haematology and serum biochemistry values pre and post treatment with Movicol were normal for most children with the exception of a few values outside the range. Only one of these results was judged to be significant by the investigator. The 6 year old patient had a plasma mean cell volume (MCV) value of 94.2 FL which was above the reference range (71.6 - 87.3 FL) following treatment with Movicol. However, her MCV was 89 FL at the beginning of the study and was thought to be unrelated to the study treatment. No action was taken and the situation was resolved by the end of the study.

Overall, 17 patients (27%) in the safety population started at least one concomitant medication during the study. The most common medication taken was paracetamol (14 children). No non-study laxative medications were started during the study.

Eleven patients (37%) reported side effects, which consisted of nausea and vomiting, headache and abdominal pain. The symptoms disappeared following dose reduction after disimpaction was achieved. All the children analysed in this study had received various treatments (in some cases more than one)

ranging from laxatives to physical treatment with enemas and manual evacuation prior to treatment with Movicol.

In the study by R Vincent and D C A Candy, Eleven patients (37%) reported side effects, which consisted of nausea and vomiting, headache and abdominal pain. The symptoms disappeared following dose reduction after disimpaction was achieved. All the children analysed in this study had received various treatments (in some cases more than one) ranging from laxatives to physical treatment with enemas and manual evacuation prior to treatment with Movicol.

The reported adverse events from published studies are consistent with the findings in the company sponsored studies.
The majority of reported adverse events are well known with this class of osmotic laxatives (e.g. nausea, and abdominal pain).

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Movicol Junior Neutral.

Safety specification

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan (for the Movicol range), version 5.2 signed 12th of May 2020 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Osmotic laxatives, including Macrogols (Polyethylene glycols), have been available in the European Union for much more than ten years. Their use is well established with recognised efficacy and acceptable safety. The data have demonstrated the efficacy and safety of the product to the extent that the overall risk/benefit of the product is favourable for the proposed indications.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The mutual recognition procedure for Movicol Junior Neutral, powder for oral solution in sachet was positively finalised on 2021-12-22.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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