CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Movicolon Liquid Sinaasappel 13.9 g/25 ml and Movicolon Liquid Orange 13.9 g/25 ml, concentrate for oral solution Norgine B.V., the Netherlands

Macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 106664, 106666

28 January 2013

Pharmacotherapeutic group:	osmotically acting laxatives
ATC code:	A06AD65
Route of administration:	oral
Therapeutic indication:	chronic or habitual constipation in adults and children over 12 years of age
Prescription status:	prescription only
Date of authorisation in NL:	6 July 2011
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Movicolon Liquid Sinaasappel 13.9 g/25 ml and Movicolon Liquid Orange 13.9 g/25 ml, concentrate for oral solution from Norgine B.V. The date of authorisation was on 6 July 2011 in the Netherlands.

The product is indicated for chronic or habitual constipation in adults and children over 12 years of age.

A comprehensive description of the indications and posology is given in the SPC.

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.

This national procedure concerns a line extension to Movicolon 13.8 g, powder for oral solution (NL License RVG 19006), which has been registered in the Netherlands by Norgine B.V. since 5 November 1996. The differences between Movicol concentrate and Movicol 13.8 g powder for oral solution are the pharmaceutical form (concentrate for oral solution rather than powder for oral solution), flavouring (orange rather than lemon and lime) and the inclusion of the excipients sucralose, purified water and preservatives.

Movicolon concentrate was developed as a convenient dosage option with a new flavor. The currently marketed Movicolon product requires the patient or caregiver to reconstitute the powder in water, which can take up to three minutes to reconstitute. In addition, offering patients a liquid formulation which is quicker to prepare was perceived to provide a benefit to patients thus resulting in improved patient compliance.

Movicolon Liquid Sinaasappel and Movicolon Liquid Orange are identical products including orange flavour (parallel submission) and only differ in the name of the product. In this report, both products are referred to as Movicolon Liquid Orange.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This application cross-references the pre-clinical and clinical data approved for Movicolon therefore these have not been resubmitted with this application. No new non-clinical or clinical studies on efficacy and safety are submitted as the active substances and pharmaceutical form on administration are essentially similar to those approved for the parent product Movicolon powder.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a line extension.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The four active components of the product are macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride. All four active components are widely used in pharmaceutical formulations and are subject to European Pharmacopoeia (Ph.Eur.*) monographs.
The manufacturers of the active substances macrogol 3350, sodium chloride, potassium chloride and sodium hydrogen carbonate possess Certificates of Suitability.

Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

This application concerns a line extension to Movicolon powder. The manufacturers mentioned for the product at issue that the active ingredients are also used for the registered powder. The manufacturing process, quality control of drug substance and stability of drug substance were assessed and accepted for Movicolon powder. All of the active components are stable materials and appropriate information regarding their stability is included in the submission. Batch analysis results for all active substances demonstration compliance with the Ph. Eur. specification have been provided. Physical characteristics such as particle size are not relevant since the substance will be dissolved in the final product.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Movicolon Liquid Orange is a viscous, clear, colourless solution.

The composition per 25 ml is:

Macrogol 3350	13.125 g
Sodium chloride	350.7 mg
Sodium hydrogen carbonate	178.5 mg
Potassium chloride	46.6 mg

The concentrate is packed in multidose 500 ml PET bottles with child resistant closure of LDPE with PE liner. A measuring device (PP) is supplied as an aid for dispensing. The bottle is sufficient for 20 dosages.

The excipients are: acesulfame potassium, sucralose, benzyl alcohol, methyl parahydroxybenzoate, ethyl parahydroxybenzoate, orange flavour (contains flavouring substances, flavouring preparations and ethanol), purified water.

The product is administered by diluting 25 ml of the concentrate with 100 ml of water. The 125 ml of solution produced will contain the same active components in the same amounts and the same quantity of

electrolyte ions as a solution formed by adding the contents of a 13.8 g sachet of Movicolon powder for oral solution to 125 ml of water.

Pharmaceutical development

The development of the product has been described; the choice of excipients and their functions are explained. The selection of the preservative benzyl alcohol was justified. Overall, a review of the available safety data for benzyl alcohol indicates no toxicological concerns at the proposed low oral daily levels of 1.3 mg/kg (chronic constipation; longer term use). No safety concern exists even in the case of off-label administration for faecal impaction (5.21 mg/kg) where the acceptable daily intake (ADI) of 5 mg/kg would be exceeded.

Movicolon concentrate has been evaluated for microbiological attributes during stability studies in accordance with the current Ph. Eur. and the product meets the required specification for aqueous preparations for oral use.

The sweeteners/flavouring used in Movicolon concentrate and their concentration were selected as providing the most palatable product following acceptability trials involving various combinations of sweeteners.

Bioequivalence studies are not required. The product is administered by diluting 25 ml of the concentrate with 100 ml of water. The 125 ml of solution produced contains the same active components in the same amounts and the same quantity of electrolyte ions as the solution formed by adding the contents of a 13.8 g sachet of Movicolon powder for oral solution to 125 ml of water. Macrogol 3350 is not absorbed. The additional excipients are not expected to affect bioavailability.

Manufacturing process

The process consists of three main standard operations: dispensing, mixing and filling. The manufacturing process is adequately described and controlled via appropriate in-process controls.

The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation. Prospective validation of the manufacturing process for Movicolon concentrate will be carried out on three consecutive batches before the drug product is placed on the market.

Control of excipients

The excipients comply with the Ph.Eur. where applicable. Sucralose complies with NF requirements, which is acceptable. Appropriate specifications have been laid down for the orange flavour.

Quality control of drug product

The product specification includes tests for description, colour of solution, pH, identification of macrogol, potassium, sodium, chloride and hydrogen carbonate, assay of the same active substances, assay of the preservatives, benzyl alcohol, methyl hydroxybenzoate and ethyl hydroxybenzoate, microbiological contamination. The shelf-life specification has adapted limits for colour of solution and assay. Identification tests and preservative assay are omitted from the shelf-life specifications and efficacy of antimicrobial preservation is added.

The analytical methods are acceptable. Batch analytical data have been provided on four full-scale batches, demonstrating compliance with the release specification.

Microbiological Attributes

Movicol concentrate is supplied in a multidose container. It contains a preservative system consisting of methyl hydroxybenzoate and ethyl hydroxybenzoate solubilised in benzyl alcohol, at a level of 0.0625 g per 25 mL. Antimicrobial preservation testing has shown this preservative system to be suitable. The product meets the specification defined in the current Ph. Eur. section 5.1.3, efficacy of antimicrobial preservation for oral solutions.

Stability of drug product

Stability studies have been carried out on four pilot batches of Movicolon concentrate, Movicolon concentrate diluted with water and Movicolon concentrate under conditions simulating use in practice (in-use stability). The stability study results for Movicolon concentrate show the drug product is within the

specification limits at long term (24 months, 30°C/65% RH) and accelerated storage conditions (6 months). Data from photostability studies show that the product is stable when exposed to light.
The product is highly stable when stored in PET bottles and therefore a shelf life of two years was granted. No special storage conditions are required prior to opening.
Additional stability data is available at 2-8°C. These data support the storage instruction 'Do not refrigerate or freeze' for the drug product.
The in-use stability data of the in multidose PET bottles were within specification when stored at 30°C/65%RH for up to 35 days. Therefore a 30 day in-use shelf-life is proposed for the opened bottles when stored in line with the storage recommendation 'Do not store above 30°C.'

The diluted solution stability data generated were within specification after being kept at 2 – 8°C and 30°C/65% RH for up to 24 hours. A 24 hour shelf-life is applicable for the diluted solution when stored in line with the storage recommendations 'Do not store above 30°C. Keep solution covered.'

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a line extension to Movicolon 13.8 g, powder for oral solution, which is available on the Dutch market. This application cross-references the non-clinical data approved for Movicolon powder. The safety evaluation of the excipients that differ from Movicolon powder is sufficiently covered by the quality assessment.
A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other Movicolon products on the market. The approval of this product will not result in an increase in the total quantity of any of the active substances released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

All four active substances are well-known with established efficacy and tolerability. This application cross-references the clinical data approved for Movicolon powder for oral solution. No new clinical studies on efficacy and safety are submitted as the active substances and pharmaceutical form on administration are essentially similar to those approved for the parent product, which is acceptable. The differences between Movicolon powder and Movicolon concentrate relate to the change in pharmaceutical form on presentation (*i.e*. a concentrated liquid instead of a powder sachet) and the introduction of some new, well-established excipients in the formulation. The currently marketed Movicolon product requires reconstitution of the powder in water, which can take up to three minutes. In addition, offering patients a liquid formulation which is quicker to make up was perceived to provide a benefit to patients thus resulting in improved patient compliance.

Benefit/risk assessment

Efficacy
The amount and type of active ingredients in Movicolon concentrate 25 ml is similar to that of Movicolon powder. Both formulations contain 13.125 g macrogol 3350 with additional electrolytes. A comparison of the content of the electrolytes in one sachet of Movicolon made up to 125 ml of solution with water versus that of 25 ml of Movicolon Orange concentrate diluted in 100 ml water is provided in Table 1 below.

Table 1: A comparison of electrolyte content in Movicol, Movicol Sinaasappel and Movicol Orange

Electrolytes	Movicolon Reconstituted powder (125 ml solution)	Movicolon Concentrate Sinaasappel Diluted solution (125 ml solution)	Movicolon Concentrate Orange Diluted solution (125 ml solution)
Sodium	65 mmol/l	65 mmol/l	65 mmol/l
Chloride	53 mmol/l	53 mmol/l	53 mmol/l
Potassium	5.4 mmol/l	5.4 mmol/l	5.4 mmol/l
Hydrogen carbonate	17 mmol/l	17 mmol/l	17 mmol/l

It is agreed that from the perspective of efficacy there should be no difference between Movicolon Concentrate and Movicolon powder. The excipients present in the Movicolon concentrate formulation (orange flavor, purified water, sucralose, and benzyl alcohol and hydroxybenzoate preservatives) but not in Movicolon are considered not to affect efficacy, which is agreed.

Safety:
Movicolon concentrate contains ingredients (orange flavour, purified water, sucralose, and benzyl alcohol and hydroxybenzoate preservatives) which are not present in the powder formulation. The excipients are all well known ingredients that are commonly used in liquid medicines. A comparison of Movicolon and Movicolon Liquid Orange Excipients is shown in Table 2.

Table 2: Comparison of Movicolon, Movicolon Concentrate Orange and Movicolon Concentrate Sinaasappel Excipients

Excipients	Movicolon (g/sachet)	Movicolon Liquid Orange (g/25ml)	Movicolon Liquid Sinaasappel (g/25ml)
Acesulfame potassium	0.0100	0.0100	0.0100
Lime and lemon flavour	0.1000	None	None
Sucralose	None	0.0030	0.0030
Orange Flavour containing: • Flavouring Substances • Flavouring Preparations • Ethyl Alcohol	None	0.0800 (0.0006) (0.0002) (0.0792)	0.0800 (0.0006) (0.0002) (0.0792)
Preservative containing: • Benzyl Alcohol • Methyl hydroxybenzoate • Ethyl hydroxybenzoate	None	0.0625 (0.0456) (0.0113) (0.0056)	0.0625 (0.0456) (0.0113) (0.0056)
Purified water	None	13.750 ml	13.750 ml

The orange and citrus flavour contains less than 100 mg alcohol per unit dose. With regard to the sucralose and the preservative components, the quantities present in the maximum dose (75 ml) likely to be given to a 70 kg adult fall within the acceptable daily intake (ADI) for all these agents (see Table 3). However, exposure to benzyl alcohol can also be expected from other sources including the use of additives and flavourings in food. As calculated by the MAH, the level of exposure for 40 kg adolescents for the indication of chronic constipation can be expected to be up to 3.42 mg/kg from Movicolon concentrate alone. Considering exposure can also be expected from other sources, the total exposure to benzyl alcohol could be expected to be above the ADI. The MAH adequately stated in the SPC that the product should not be used in the paediatric population and refers to suitable paediatric formulations.

Table 3: Amount of excipients and ADI (Chronic constipation)

Excipient	ADI mg/kg	Amount (mg) for 25 ml dose, 3 times/day for 70 kg adult	Amount (mg) for 25 ml dose, 3 times/day for 40 kg adolescent
Methyl hydroxybenzoate	0-10 [1]	11.3 x 3 / 70 = 0.48 mg/kg	11.3 x 3 / 40 = 0.85 mg/kg
Ethyl hydroxybenzoate	0-10 [1]	5.6 x 3 / 70 = 0.24 mg/kg	5.6 x 3 / 40 = 0.42 mg/kg
Benzyl alcohol	0-5 [2]	45.6 x 3 / 70 = 1.95 mg/kg	45.6 x 3 / 40 = 3.42 mg/kg
Sucralose	0-15 [3]	3.0 x3 / 70 = 0.13mg/kg	3.0 x 3 /40 = 0.23 mg/kg

NOTE: Based on the maximum daily dose of MOVICOL Concentrate (25 ml three times daily).

If this product were to be given in the dose volume required to treat faecal impaction (200 ml) there might be some additional risks with potential for fluid loss and dehydration, particularly in frail elderly patients and children, and the potential for exceeding the ADI for benzyl alcohol if given to children for constipation and to children or adults for faecal impaction (see Table 4). By restricting the indications to chronic constipation in adults and the elderly, the MAH has minimized these risks.

Table 4: Amount of excipients and ADI (faecal impaction)

Excipient	ADI mg/kg	Amount (mg) for 25 ml dose, 8 doses/day for 70 kg adult	Amount (mg) for 25 ml dose, 8 doses/day for 40 kg adolescent
Methyl hydroxybenzoate	0-10 [1]	11.3 x 8 / 70 = 1.29 mg/kg	11.3 x 8 / 40 = 2.26 mg/kg
Ethyl hydroxybenzoate	0-10 [1]	5.6 x 8 / 70 = 0.64 mg/kg	5.6 x 8 / 40 = 1.12 mg/kg
Benzyl alcohol	0-5 [2]	45.6 x 8 / 70 = 5.21mg/kg	45.6 x 8 / 40 = 9.12 mg/kg
Sucralose	0-15 [3]	3.0 x 8 / 70 = 0.34 mg/kg	3.0 x 8 /40 = 0.6 mg/kg

NOTE: Based on the maximum daily dose of MOVICOL Concentrate (25 ml eight doses daily).

Misuse

There is a possibility that a patient may drink the concentrated solution without diluting in water, either by mistake or deliberately. The latter is difficult to prevent, adequate warning is included **"This product must not be taken undiluted."** in the PIL to minimize the chance of patients inadvertently taking the product without dilution. This warning should be more obvious in the PIL and label. The MAH agreed to include the warning in the PIL first under the heading **'**How to take Movicolon Liquid Orange concentrate'. This also applies to the label where this warning statement now appears immediately under the heading 'Dosage'.
In case of accidental intake of the undiluted solution in the recommended dose for chronic constipation, a theoretical net loss of water may occur because of the intake of a hyper-osmotic solution. Although especially elderly are susceptible for the effects of potential fluid loss and dehydration, in practice this extraction of water is assumed to be of little consequence at the recommended low dose for constipation. Moreover accidental intake of undiluted product would easily be recognized by patients since the amount of flavouring and sweetening agents present in the concentrated Movicolon Liquid solution would cause a rather unpleasant taste and a sensation of thirst which will urge the patients to drink additional water.

Another potential misuse that needs to be addressed concerns the risk of inadvertently using the product for the treatment of faecal impaction, although not indicated. A confusion with the different Movicolon preparations may occur, especially as also for Movicolon powder a variation with a special flavor (Movicolon Chocolate powder) exists.

The MAH has taken measures to minimize these risks. This includes a change in product name (Movicolon Liquid instead of Movicolon concentrate), an explicit statement in section 4.2. that the product is not recommended in faecal impaction and an additional warning in section 4.4. regarding the presence of benzyl alcohol and a recommendation not to exceed the stated dose.

Overall benefit/risk balance

The amount and type of active ingredients in Movicolon Liquid Orange 13.9 g/25 ml is similar to that of the licensed Movicolon powder, as is the dosing regimen for the proposed indication “treatment of chronic constipation”. Therefore, efficacy can be extrapolated from the licensed product to the new formulation. The difference in excipients between both formulations is not considered to affect efficacy. Also, the product is considered safe in the proposed dose in the adult population; the quantities of excipients (especially benzyl alcohol) present in the maximum dose fall within the acceptable daily intake (ADI) for all these agents. However, there is a potential for confusion with the different Movicolon preparations if the products in the range have different indications. The Movicolon concentrate products are likely, in practice, to be used interchangeably with Movicolon powder even for the indication faecal impaction. Also, the risk of exposure to benzyl alcohol in these products and the risk of fluid loss and dehydration in a vulnerable group of patients was taken into account. Appropriate warnings were included in the product information.

Overall, the benefit/risk balance for Movicolon Liquid Orange 13.9 g/25 ml is considered positive.

Risk management plan

There is now more than 10 years post-authorisation experience with the active substances. The safety profile of macrogol 3350, sodium chloride, sodium hydrogen carbonate and potassium chloride can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the national procedure is in accordance with that accepted for Movicolon powder for oral solution.

Readability test

For readability testing, reference was made to the previously user tested PIL for Movicolon Chocolate 13.9 g sachet, powder for oral solution. This leaflet is similar enough to the non-tested PIL for Movicolon Liquid Orange 13.9 g/25 ml, concentrate for oral solution, so that a combination of bridging and a focus test suffices for demonstrating the readability for Movicolon Liquid Orange.

Although similar, there are aspects of the Movicolon Liquid Orange PIL which are not addressed in the Movicolon Chocolate PIL. Given this, a focus test was conducted to address those aspects of the Movicolon Liquid Orange PIL which are not addressed in the bridging report.

The focus test consisted of a pilot round with 2 participants, followed by two rounds with 10 participants each. Both rounds of testing showed that, for each question, 100% of participants were able to find the correct information, and 100% of participants were able to answer the questions correctly.

The focus test has been sufficiently performed. Readability is considered demonstrated for Movicolon Liquid Orange.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Movicolon Liquid Sinaasappel 13.9 g/25 ml and Movicolon Liquid Orange 13.9 g/25 ml, concentrate for oral solution have a proven chemical-pharmaceutical quality and are approvable line extensions to Movicolon 13.8 g, powder for oral solution. Movicolon powder is a well-known medicinal product with an established favourable efficacy and safety profile.

No new non-clinical or clinical studies on efficacy and safety are submitted as the active substances and pharmaceutical form on administration are essentially similar to those approved for the parent product Movicolon powder.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of Movicolon powder. The SPC, package leaflet and labelling are in the agreed templates.

In the Board meeting of 15 April 2010, the risk of exceeding the ADI for benzyl alcohol with use in faecal impaction was discussed.

The MEB, on the basis of the data submitted, considered that efficacy and safety have been demonstrated, and has therefore granted a marketing authorisation. Movicolon Liquid Sinaasappel 13.9 g/25 ml and Movicolon Liquid Orange 13.9 g/25 ml, concentrate for oral solution were authorised in the Netherlands on 6 July 2011.

The following post-approval commitments were made during the procedure.

Quality - medicinal product

- The MAH committed to complete the dossier with the obtained in-use stability data with a batch at the end of its shelf-life in support of the in-use shelf-life of 30 days. This commitment has been fulfilled.
- The MAH committed to re-evaluate the preservative system and optimise the level of benzyl alcohol present. This commitment has been fulfilled.

List of abbreviations

ADI	Acceptable Daily Intake
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in test procedure for an excipient.	--	IB	5-9-2011	4-10-2011	Approval	N
Post-approval commitment: responses to remaining points for clarification that may be resolved after approval.	--	PAC	4-10-2011	15-12-2011	Approval	N
Update of the European Pharmacopoeial CEP or the active substance sodium hydrogen carbonate.	--	IA	26-3-2012	30-3-2012	Approval	N
Submission of a new or updated Ph. Eur. certificate of suitability: new certificate for a new manufacturer.	--	IA	1-8-2012	3-9-2012	Approval	N
Harmonisation of the dosing instructions in the SmPC with those of the reference product Movicolon 13.8 g (RVG 19006). Clarification of the age limit for children in the SmPC.	--	IB	4-10-2012	30-11-2012	Approval	N
Changes to an existing pharmacovigilance system as described in the Detailed Description of the Pharmaco-vigilance system.	--	IA/G	31-10-2012	16-11-2012	Approval	N