2.3.P.1 Description and Composition of the Drug Product

2.3.P.1.1 Description of the Dosage Form

Microlax is a colourless, viscous solution containing small air bubbles, single-dose preparation filled in a 5ml polyethylene tube.

2.3.P.1.2 Composition of the Drug Product

Full details of the composition are provided in Table 2.3.P.1- 1.

Table 2.3.P.1- 1 Composition of Microlax 5mL Rectal Solution

Name of Ingredient	Unit Formula (mg/mL)	Function	Reference to Standards[2]
Active Ingredients			
Sodium citrate	90.0	Active	Ph. Eur.
Sodium Lauryl Sulfoacetate[1](70%)	12.9	Active	Internal Monograph
Sorbitol, Liquid (crystallizing)	893.0	Active	Ph. Eur.
Other ingredients			
Sorbic acid	1.0	Preservative	Ph. Eur.
Glycerol	125.0	Thickener	Ph. Eur.
Purified Water	to 1 mL	Solvent	Ph. Eur.

[1] Formula is established with a theoretical content of 70%. The quantity introduced per batch is adjusted according to assay result.

[2] The current edition of the European monograph is applied. Any additional or subsequent changes in the monograph will be adhered to.

2.3.P.1.3 Overages

Not applicable.

2.3.P.1.4 Container and Closure

The container is comprised of a white plastic tube with cannula and twist off seal made from low density polyethylene (LDPE). The tube is placed in an outer carton.

2.3.P.2 PHARMACEUTICAL DEVELOPMENT

The Microlax® formulation was developed more than forty years ago when it was found that the addition of sodium citrate to certain thick suspensions, used as X-ray contrast agents for investigations of the colon, could essentially eliminate constipation. On further investigation it was subsequently found that sodium citrate acts in a similar way also on hard faeces, causing a pronounced mollifying effect. Thus, the basis for the development of a rectal solution with targeted effect directly on the hardened faeces was at hand. There were three major advantages in comparison to the existing therapy available at that time Firstly, the irritating side effect on the bowel, commonly encountered with stimulant-type laxatives, was essentially avoided. Secondly, onset of action was fast, usually within 5 to 15 minutes. Thirdly, a single dose of only 5 mL was required, thus making self-administration viable.

This approach for symptomatic therapy for constipation in the lower end of the intestinal tract was clearly a new one and consequently a patent was granted in 1965 (US Patent No. 3,211,614).

Drug substances

The drug product contains the active ingredients Sodium Citrate, Sodium Lauryl Sulfoacetate and Sorbitol.

The quality of the active substances is controlled by the supplier and finished product manufacturer specifications in line with the Pharmacopoeial Monographs and the Certificate of Suitability requirements for Sorbitol.

Excipients

The excipients present in the proposed formulation have a history of use in pharmaceutical compositions and were chosen based on their compatibility with the active substances and other excipients, their functionality and in consideration of their well-documented safety profiles. Composition details are provided in section 3.2.P.1. All excipients are of pharmacopoeial quality.

Formulation development

On the basis of the observation of the action of sodium citrate, a small volume rectal solution was formulated. Sorbitol proved to be a suitable vehicle. A surface-active agent was incorporated to improve wetability of the formulation, in this way enhancing overall effectiveness. Sodium lauryl sulfoacetate was found most suitable for this purpose. Small amounts of glycerol were included to promote solubility of the other ingredients. In addition, glycerol is also conducive to the consistency of the rectal solution. The formulation is preserved with sorbic acid, the efficacy of antimicrobial preservation has been confirmed with microbiological challenge test. The formulation is preserved with sorbic acid and the efficacy of antimicrobial preservation has been confirmed with a microbiological challenge test (see section 3.2.P.2.5).

The final formulation consists of well-documented and widely used pharmaceutical ingredients in such proportions as to give a stable product from the manufacturing process developed.

Physicochemical and Biological Properties

The basis for the laxative effect of Microlax® is the direct action of sodium citrate on hard faecal matter causing a pronounced mollifying agent. This has been explained as due to sodium citrate penetrating the material and liberating bound water as a consequence of ion-exchange reactions. This process is referred to as peptisation. Even the hardest faeces contain substantial amounts of bound water and will thus be subject for treatment. Sodium citrate has been categorized as a peptisizer.

The surface-active agent sodium lauryl sulfoacetate gives the formula improved wetting and penetration ability, thereby enhancing overall effectiveness. The ingredient has been categorized as a wetting agent.

Sorbitol is the major vehicle ingredient but is also considered to promote the peptisation process. It is therefore categorized as both vehicle and enhancer of peptisation. All other ingredients of Microlax® (i.e. glycerol, sorbic acid and purified water) are formulation components; added to yield a stable product well suited to its purpose.

In summary, Microlax® exerts its actions locally by altering the consistency of hardened faecal matter from the physico-chemical action of primarily sodium citrate, with sodium lauryl sulfoacetate and sorbitol promoting the process in different ways. Thus, these three ingredients are considered as active, but it should be noted that their action is of a purely physico-chemical nature rather than an explicit pharmacological one normally associated with the term active ingredient of a drug product.

Container closure system

The materials used in the proposed packaging are widely used in packaging of pharmaceutical products and have been found suitable for a wide range of products. Therefore, specific development studies are not considered necessary. Stability testing of the product has been carried out in the pack proposed for the marketed product and is reported in 3.2.P.8.

Microbiological Attributes

The microbiological testing regime adopted for the active substance, excipients, process, packaging and drug product follow the requirements of the relevant monographs of the current edition of the European Pharmacopoeia.

A study of the efficacy of antimicrobial preservation of the drug product was performed as a batch (Batch XI017) showed low concentrations of preservative in a commercial stability test after 48 months at 25°C/60% RH (0.89 mg/mL sorbic acid) and 30°C/40% RH (0.87 mg/mL sorbic acid). The specification limits for sorbic acid are 0.90 – 1.10 mg/mL. The stability study was conducted up to and including 60 months.

The drug product container is not intended for multi-dose purposes. The acceptance criteria stated in the European Pharmacopoeia for antimicrobial effectiveness testing express the recommended efficacy to be achieved. Furthermore, it is stated that the preservative properties are adequate if there is a significant fall or no increase in the number of microorganisms in the preparation. The recommendations apply particularly to multi-dose containers. In the present study there are significant reductions in the viable counts in all bacterial and yeast challenges. The mould, *A. niger*, however does not show a reduction. The mould count is stable throughout the study. Thus, there is no growth of *A. niger* in the drug product. This study shows that with an in-specification initial microbial count no growth will occur that will present a hazard to the patient from either infection or spoilage.

Microbial testing is conducted on finished product batches at release and at shelf-life.

Compatibility

Not applicable as there are no reconstitution diluents(s) or dosage devices associated with the use of the drug product.

2.3.P.3 MANUFACTURE

2.3.P.3.1 Manufacturer(s)

The following table Table 2.3.P.3-1 lists the site that has responsibilities in the production of Microlax Rectal Solution and its specified functions.

Table 2.3.P.3-1. Sites and Responsibilities for Microlax Rectal Solution

Site	Responsibilities
Famar Orléans 5, avenue de Concyr 45071 Orléans Cedex 2 FRANCE	Manufacturing, packaging, quality control, and QP release

2.3.P.3.2 Batch Formula

The batch formula and size are reflected in the following table.

Table 2.3.P.3-2. Batch Formula(s) for the Manufacture of Microlax Rectal Solution

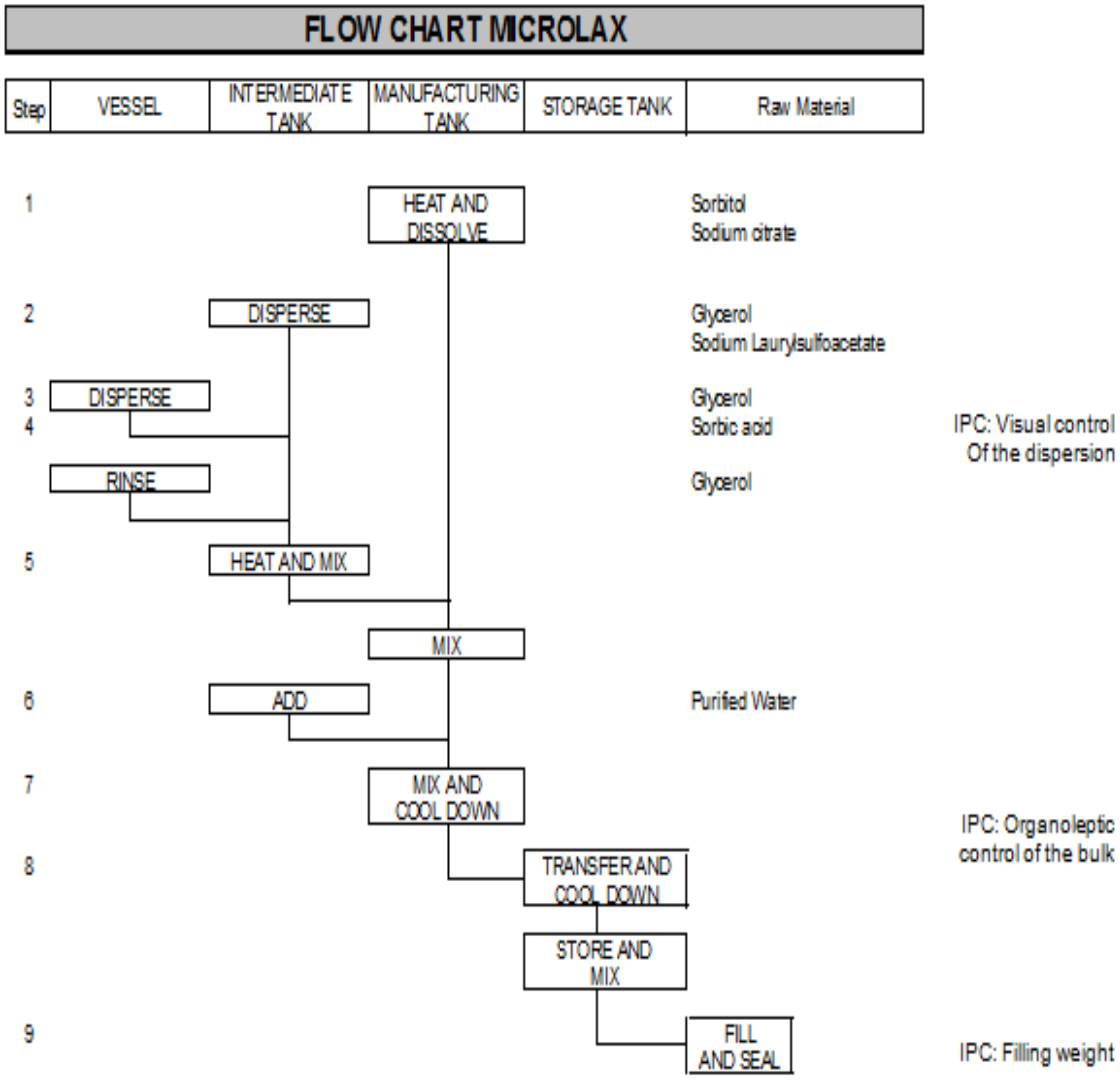
Names of Ingredients	Batch size 3000 L	
	Unit Formula	Batch Formula
Active ingredients:		
Sodium citrate	90.0 mg/mL	270 kg
Sodium lauryl sulfoacetate (70%)[1]	12.9 mg/mL	38.7 kg
Sorbitol liquid (crystallizing)	893.0 mg/mL	2679 kg
Other ingredients:		
Sorbic acid Glycerol Purified water	 1.0 mg/mL 125.0 mg/mL to 1 mL	 3.0 kg 375 kg to 3000 L

[1] Formula is established with a theoretical content of 70%. The quantity introduced per batch is adjusted according to assay result.

2.3.P.3.3 Description of Manufacturing Process and Process Controls

A flow diagram describing the proposed commercial scale operations involved in the manufacture of Microlax Rectal Solution is shown below in Figure 2.3.P.3-1.

Figure 2.3.P.3-1. Flow Chart of Manufacturing Process for Microlax Rectal Solution



2.3.P.3.4 In-Process Control for Filling Processes

Control	*Requirements*	*Method*
Filling weight	8.2- 9.1 g/5ml tube	Weighing

2.3.P.3.5 Process Validation and/or Evaluation

Process validation was performed on three batches manufactured at Famar Orléans i.e. batches 0504027 (=G25-04A R01), 0504238 (=G25-04A R02) and 0506461 (=G25-04A R03) with a batch size of 3000 L. The table below lists the details regarding the batches used for process validation.

Batch Number	0504027	0504238	0506461
Date of Manufacture	05/07/05	19/07/05	02/11/05
Site of Manufacture	Famar Orléans	Famar Orléans	Famar Orléans
Batch Size	3000 L	3000 L	3000 L

The objective was to check the critical steps of the process, and to demonstrate that the process is well controlled and reproducible.

At each stage of the process, checks were carried out to ensure completion of the step.

As the in-process controls and analytical results on blend and finished product meets specifications, the manufacturing process is considered satisfactory, reproducible and well controlled.

2.3.P.4 CONTROL OF EXCIPIENTS

2.3.P.4.1 Specifications

Excipients Described in a Pharmacopoeia

Compendial excipients identified in 3.2.P.1 Description and Composition of the Drug Product are tested and released in accordance with the specifications and test methods described in the referenced Pharmacopoeia.

Ingredients	Specification
Glycerol	Ph. Eur..[1]
Sorbic acid	Ph. Eur..[1]
Purified water	Ph. Eur.[1]

[1] The current edition of the European monograph is applied. Any additional or subsequent changes in the monograph will be adhered to.

Typical certificates of analysis for the pharmacopoeial excipients are provided in Module 3.2.P.4.1.

Excipients Not Described in a Pharmacopoeia

Not applicable.

2.3.P.4.2 Analytical Procedures

Excipients Described in a Pharmacopoeia

The ingredients are analysed using the procedures specified in their respective compendial monographs.

Excipients Not Described in a Pharmacopoeia

Not applicable.

2.3.P.4.3 Validation of Analytical Procedures

Not applicable. The analytical procedures used are those described in the European pharmacopoeia.

2.3.P.4.4 Justification of Specifications for Excipients

The specifications for compendial excipients are justified by the fact that they are compendial.

2.3.P.4.5 Excipients of Human or Animal Origin

No excipient from animal origin is used in the manufacture of Microlax solution, as declared in the statement provided in Module 3.2.P.4.5.

2.3.P.4.6 Novel Excipients

There are no novel excipients used in the manufacture of Microlax Rectal Solution.

2.3.P.5.1 Specification(s)

Specifications at release and end of shelf-life are summarized below in Table 1 and Table 2 respectively.

Table 1 Release Specification(s)

Test Name	Test Method	Acceptance Criteria
Description	Visual inspection	A colourless, viscous solution containing small air bubbles.
Identification:		
Sodium lauryl sulphoacetate	Visual	Positive colour reaction
Sodium citrate	Visual	Positive colour reaction
Sorbitol	TLC	Rf-value matches standard
Tests		
Deliverable volume	Weighing	Volume not less than stated on the label
Density, after de-aeration	Density meter	1.25 – 1.31 g/ml
pH, Initial	Ph Eur. 2.2.3	6.0 – 8.0
Uniformity of dosage units (mass variation)1	Ph.Eur. 2.9.40	Complies
Assay:		
Sodium lauryl sulphoacetate, Initial	Potentiometric Titration	8.5 – 9.5 mg/ml
Sodium citrate, Initial	Potentiometric Titration	85 – 95 mg/ml
Sorbitol, Initial	Polarimetric or HPLC (alternate method)	594 – 656 mg/ml
Sorbic acid, Initial	UV-spectrophotometry	0.90 – 1.10 mg/ml
Microbiological quality		
Total Aerobic Microbial Count (TAMC)	Ph Eur. 2.6.12	NMT 2000 CFU/ml
Total Yeast and Moulds Count (TYMC)	Ph Eur. 2.6.12	NMT 200 CFU/ml

Table 2 Specification(s) at end of Shelf-Life

Test Name	Test Method	Acceptance Criteria
Description	Visual inspection	A colourless, viscous solution containing small air bubbles.
Identification[1]:		
Sodium lauryl sulphoacetate	Visual	Positive colour reaction
Sodium citrate	Visual	Positive colour reaction
Sorbitol	TLC	Rf-value matches standard
Tests		
Deliverable volume	Weighing	Volume not less than stated on the label
Density, after de-aeration	Density meter	1.25 – 1.31 g/ml
pH, Stability	Ph Eur. 2.2.3	6.0 – 8.0
Assay:		
Sodium lauryl sulphoacetate, Stability	Potentiometric Titration	8.5 – 9.5 mg/ml
Sodium citrate, Stability	Potentiometric Titration	87 – 96 mg/ml
Sorbitol, Stability	Polarimetric or HPLC (alternate method)	594 – 656 mg/ml
Sorbic acid, Stability	UV-spectrophotometry	≥ 0.90 mg/ml
Microbiological quality		
Total Aerobic Microbial Count (TAMC)	Ph Eur. 2.6.12	NMT 2000 CFU/ml
Total Yeast and Moulds Count (TYMC)	Ph Eur. 2.6.12	NMT 200 CFU/ml

[1] As the identification tests are not a stability indicating, they are not monitored throughout the stability program.

2.3.P.5.2 Analytical Procedures

Microlax contains three different active components: sodium citrate, sodium lauryl sulphoacetate and sorbitol. There is also a preservative added: sorbic acid. In addition the product contains water and glycerol. There are separate assay methods for each of the active components and the preservative.

2.3.P.5.2.1 pH

Refer to Ph. Eur. method n° 2.2.3, current edition.

2.3.P.5.2.2 Deliverable Volume

The deliverable volume is determined by weighing the content of one tube.

2.3.P.5.2.3 Microbiological quality

Refer to Ph. Eur. method n° 2.6.12, current edition.

2.3.P.5.2.4 Density

Density is measured by injection of a sample preparation into a densimeter cell and reading at a temperature of 20 ° C.

2.3.P.5.2.5 Identification of Sodium Laurylsulphoacetate

Sodium Lauryl Sulfoacetate is identified by a colorimetric method.

2.3.P.5.2.6 Identification of Sodium Citrate

Sodium Citrate is identified by a colorimetric method.

2.3.P.5.2.7 Identification of Sorbitol and Sorbic Acid

Sorbitol and Sorbic acid are identified by a Thin Layer Chromatography method, with reading under UV-light at 254 nm.

The Rf-value obtained from the sample solution must not differ more than ± 0.02 from the Rf- value obtained from the standard solution to be accepted.

2.3.P.5.2.8 Assay of Sodium Lauryl Sulfoacetate

Sodium Lauryl Sulfoacetate is determined by Potentiometric titration method.

Ionic surfactant electrode (Ag/ AgCl) is used with titrant Benzethonium chloride solution.
1 ml of 0.004M Benzethonium chloride solution is equivalent to 1.38 mg of anionic-active matter.

2.3.P.5.2.9 Assay of Sodium Citrate

Sodium Lauryl Sulfoacetate is determined by a Potentiometric titration method. An electrode for non-aqueous applications is used with titrant Perchloric acid.

2.3.P.5.2.10 Assay of Sorbic Acid

Sorbic acid is determined by UV-spectrophotometry method, at 262 nm. The absorbance of the sample solution is measured against the blank solution.

2.3.P.5.2.11 Assay of Sorbitol

Sorbitol is determined by Polarimetric method (angular rotation) or by HPLC method (alternative method).

2.3.P.5.2.12 Uniformity of mass

Refer to current edition of Ph. Eur. Method n° 2.9.40, Mass Variation for Liquid or Semisolid dosage forms.

2.3.P.5.3 Validation of Analytical Procedures

2.3.P.5.3.1 Validation of HPLC Method for the Assay of Sorbitol

A summary of the validation results is presented in the table below.

Validation Elements	Internal Specifications	Results of Proposed Method
SPECIFICITY	No interference	**No interference**
LINEARITY	$r^2 > 0.995$	**1.000**
ACCURACY	98 ≤ % recovery ≤ 102 % (for each concentration and for average value)	80%: **99.9%** 100%: **99.8%** 120%: **100.1%** Average: **100.0%**
PRECISION Repeatability Intermediate Precision	 ≤ 2 % ≤ 2 %	 **0.1%** **0.6%**
RANGE	NA	**80 – 120 %** (of theoretical concentration)

Conclusion:

All results obtained are in compliance with the acceptance criteria.

The proposed method is specific, linear, accurate and precise.
The HPLC method for Sorbitol assay in MICROLAX solution can be considered as validated and therefore be used for the finished product quality control at release as well as for stability studies.

2.3.P.5.3.2 Validation of Potentiometric titration method for the assay of Sodium Lauryl Sulfoacetate

A summary of the validation results is presented in the table below.

Validation Elements	Internal Specifications	Results of Proposed Method
SPECIFICITY	No interference	**No interference**
LINEARITY	$r^2 > 0.995$	**1.000**
ACCURACY	98 ≤ % recovery ≤ 102 % (for each concentration and for average value)	80%: **101.7%** 100%: **100.9%** 120%: **100.5%** Average: **101.0%**
PRECISION Repeatability Intermediate Precision	 ≤ 2 % ≤ 2 %	 **1.5%** **1.3%**
RANGE	NA	**80 – 120 %** (of theoretical concentration)

Conclusion:

All results obtained are in compliance with the acceptance criteria.

The proposed method is specific, linear, accurate and precise.
The potentiometric method for Sodium lauryl sulfoacetate assay in MICROLAX Solution can be considered as validated and therefore be used for the finished product quality control at release as well as for stability studies.

2.3.P.5.3 Validation of UV Spectrophotometric Method for the Assay of Sorbic Acid

A summary of the validation results is presented in the table below.

Validation Elements	Internal Specifications	Results of Proposed Method
SPECIFICITY	No interference	**No interference**
LINEARITY	$r^2 > 0.995$	**1.000**
ACCURACY	$97 \leq$ % recovery ≤ 103 % (individual and average value)	range **99.6 to 102.6%** Average: **101.3%**
PRECISION Repeatability	≤ 2 %	**0.7%**
Intermediate Precision	≤ 2 %	**1.3%**
RANGE	NA	**50 – 150 %** (of theoretical concentration)

Conclusion:

All results obtained are in compliance with the acceptance criteria.

The proposed method is specific, linear, accurate and precise.
The UV Spectrophotometric method for Sorbic Acid assay in MICROLAX Solution can be considered as validated and therefore be used for the finished product quality control at release as well as for stability studies.

2.3.P.5.3.4 Validation of Titration Method for the Assay of Sodium Citrate

A summary of the validation results is presented in the table below.

Validation Elements	Internal Specifications	**Results of Proposed Method**
SPECIFICITY	No interference	**No interference**
ACCURACY	98 ≤ % recovery ≤ 102% (individual and average value)	range **98.5 to 102.1%** Average: **100.1%**
PRECISION Repeatability Intermediate Precision	 ≤ 2% ≤ 2%	 **0.1%** **0.2%**
RANGE	NA	**50 – 150 %** (of theoretical concentration)

Conclusion:

All results obtained are in compliance with the acceptance criteria.

The proposed method is specific, accurate and precise.
The potentiometric method for Sodium Citrate assay in MICROLAX Solution can be considered as validated and therefore be used for the finished product quality control at release as well as for stability studies.

2.3.P.5.3.5 Validation of Identification Method for Sodium Lauryl Sulphoacetate, Sodium Citrate, Sorbitol and Sorbic Acid

A summary of the validation results is presented in the tables below.

Qualitative determination of Sodium Lauryl Sulphoacetate in Microlax

Microlax Batch Numbers	Results
DG066	Blue
DF421	Blue
CL221	Blue
DF186	Blue
DF351	Blue
DGS0152 (Placebo)	Not blue

Qualitative determination of Sodium Citrate in Microlax

Microlax Batch Numbers	Results
DG066	Coloured
DF421	Coloured
CL221	Coloured
DF186	Coloured
DF351	Coloured
DFS0149 (Placebo)	Not coloured

Qualitative determination of Sorbitol and Sorbic acid in Microlax

Microlax Batch Numbers	Sorbic Acid		Sorbitol	
	Distance (mm)	Rf	Distance (mm)	Rf
Reference	74	0.90	6	0.07
CL221	74	0.91	6	0.07
DF186	73	0.91	6	0.08
DF351	72	0.91	6	0.08
DF421	70	0.91	6	0.08
DG066	69	0.91	6	0.08
Placebo BLS0122	66	0.89	-	
Placebo DSG0155	-	-	6	0.08

2.3.P.5.3.6 Validation of Microbiology Method:

The method validation report for microbiology method is provided in section 3.2.P.5.3.

Conclusion:

All results obtained are in compliance with the acceptance criteria.

The proposed methods are specific.

The colorimetric identity methods for Sodium Lauryl Sulphoacetate and Sodium Citrate in Microlax Solution can be considered as validated and therefore be used for the finished product quality control at release as well as for stability studies.

The TLC identity method for Sorbitol and Sorbic acid in Microlax Solution can be considered as validated and therefore be used for the finished product quality control at release as well as for stability studies.

2.3.P.5.4 Batch analysis

The Table 3 below lists the details regarding the batches used for analysis. Analytical results from a total of 3 batches of Microlax solution produced on full manufacturing scale are provided below in Table 4.

Table 3: Details for batches used for analysis

Batch Number	F1874R	F2107R	F2110R
Date of Manufacture	18/04/14	19/04/14	19/04/14
Date of analysis:	29/04/14	03/05/14	03/05/14
Site of Manufacture	Famar Orléans	Famar Orléans	Famar Orléans
Batch Size	3000 L	3000 L	3000 L
Use of Batch	Commercial	Commercial	Commercial

Table 4: Batch analysis results

Test	Limits	Batch No.		
		F1874R	F2107R	F2110R
Description	A colourless, viscous solution containing small air bubbles	Pass test	Pass test	Pass test
Identifications				
Sodium lauryl sulphoacetate	Positive colour reaction	Pass test	Pass test	Pass test
Sodium citrate	Positive, colour reaction	Pass test	Pass test	Pass test
Sorbitol	R_f value matches standard	Pass test	Pass test	Pass test
Tests				
Deliverable volume	Volume NLT stated on the label	Pass test	Pass test	Pass test
Density, after de-aeration	1.25-1.31 g/mL	1.29	1.28	1.29
pH	6.0- 8.0	6.8	6.7	6.7
Assays				
Sodium lauryl sulphoacetate	8.5- 9.5 mg/mL	9.1	9.2	9.1
Sodium citrate	85-95 mg/mL	91	91	92
Sorbitol	594- 656 mg/mL	634	631	639
Sorbic acid	0.90- 1.10 mg/mL	0.93	0.95	0.99
Microbiological quality				
Total Aerobic Microbial Count (TAMC)	NMT 2000 CFU/ml	Pass test	Pass test	Pass test
Total Yeast and Moulds Count (TYMC)	NMT 200 CFU/ml	Pass test	Pass test	Pass test

Three batches have been analyzed for 'Uniformity of dosage units' and the results are given in Table 5.

Table 5: Batch analysis results for 'Uniformity of mass'

Test	**limits**	**Batch numbers**		
		0H6474A	**0H6513A**	**0H6522A**
Uniformity of dosage units	Complies with the specification (EP 2.9.40)	Complies	Complies	Complies

2.3.P.5.5 Characterization of Impurities

There are no additional impurities in the finished product, other than those specified in the drug substance specifications.

2.3.P.5.6 Justification of Specifications

The specifications, both release and stability, provide adequate control of the product released to market. The parameters tested in conjunction with the in process control testing ensure that the correct drugs at the right dose are administered in a constant manner and that the product will continue to do so throughout its registered shelf-life.

Particular emphasis is placed on the quantity of drug substances delivered, through the assay values. For stability studies the assay value for each of the APIs is used for the detection of any adverse trends. The remaining tests address physical parameters including pH, density and deliverable volume.

The routine testing performed also ensures adequate control of any microbiological contamination.

European Pharmacopoeia Testing Requirements

The microbiological testing enumeration (2.6.12) is in accordance with the Ph. Eur. and general text on microbiological quality (5.1.4) for preparations for rectal administration.

ICH Q6A Guideline Testing Requirements

The ICH Q6A guideline requirement for description of product, assay and identity has been met, to ensure a product of acceptable quality is produced.

All specification clauses and associated limits applied have been set based on the experience gained during the development of the product, the manufacture of the stability batches and the data available to date.

2.3.P.6 REFERENCE STANDARDS OR MATERIALS

For Quantitative determinations for Microlax solution: quantitative determination of Sorbitol Sorbic acid and Glycerol.

- Sorbitol standard, Sorbic acid standard and Glycerol.

No other standards are described in the other methods.

2.3.P.7 CONTAINER CLOSURE SYSTEM

2.3.P.7.1 Container Description

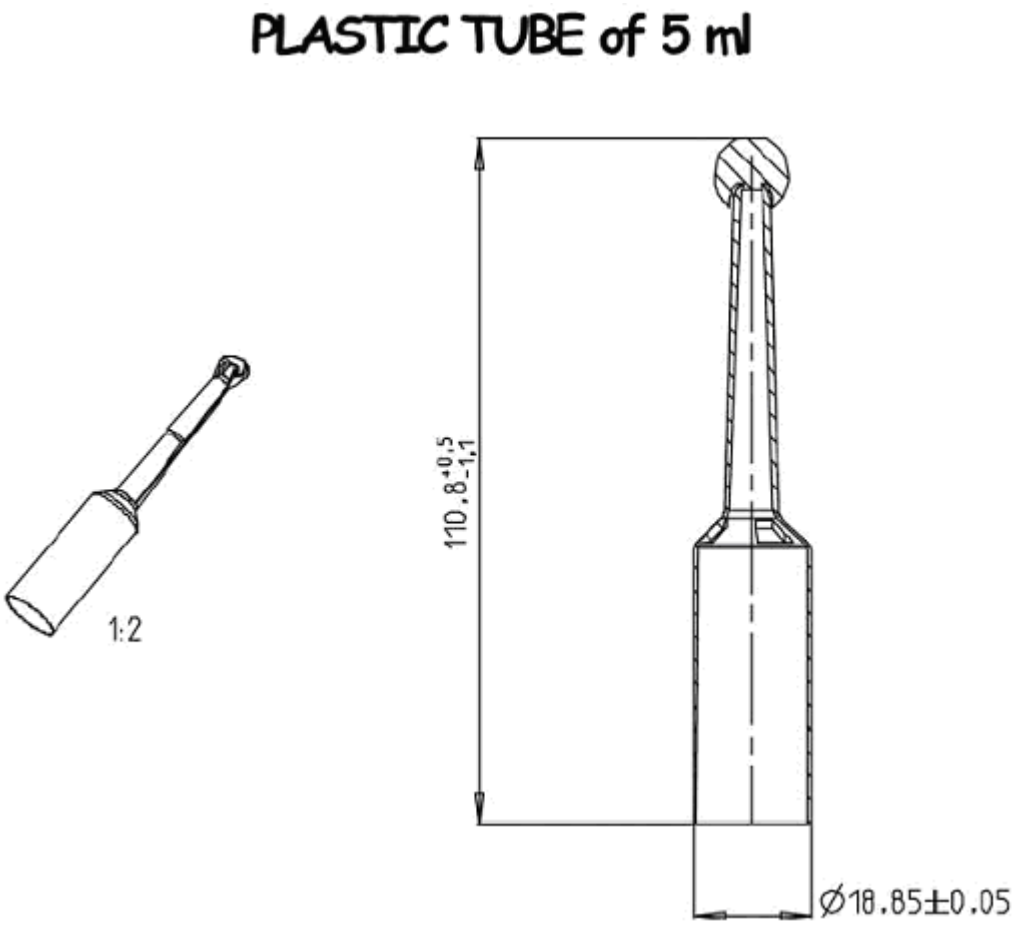
Description: White plastic tube with cannula and twist off seal

Material: Low Density Polyethylene (LDPE)

Color: White

Dimensions:According to drawings -drawing n°1 for the tube of 5 ml

Packaging material details are provided in the section 3.2.P.7.1 as typical examples of the packaging material. However, the applicant proposes to use other grades of material, provided it is of the equivalent quality.



2.3.P.7.2. Specifications

Test	Acceptance criteria	Test method
Appearance	Clean and without damage. No dimensional defects or splits	Visual inspection
Identification	To comply with reference spectrum	IR spectroscopy
Total height	To comply with drawing	Measurment
Outside diameter (body of the tube)	To comply with drawing	Measurment

2.3.P.7.3. Test Method

Identification with Infrared spectroscopy by Transmission:

- Press a piece of the sample to a thin plate.
- Record a background spectrum between 4000 and 650cm^{-1}
- Place the sample in the sample holder and place the sample holder in the spectrophotometer.
- Record a sample spectrum between 4000 and 650cm^{-1}.
- Compare the sample spectrum with the reference spectrum stated in the control instruction.
- The sample spectrum and the reference spectrum shall correspond.

2.3.P.8 STABILITY

2.3.P.8.1 Stability Summary and Conclusion

Batches 0602072, 0606458 and 0606459 have been followed in stability in compliance with ICH conditions.

Batch Nr	Batch 0602072	Batch 0606458	Batch 0606459
Batch size	3000 L		
Packaging	5 mL white LDPE plastic tubes		
Manufacturing site	Famar Orléans (Orléans, France)		
Use of batch	Stability study Commercial use		
Manufacturing date	April 2006	December 2006	December 2006
Initial date	May 2006	December 2006	December 2006

Details of the stability protocol for batches 0602072, 0606458 and 0606459 are outlined in the table below.

Periods	Conditions of storage		
	25°C/60%RH	30°C/65%RH	40°C/25%RH
Initial	TM	TM	TM
3 months	T	T	T
6 months	T	T	T
9 months	T	T	N/A
12 months	T	T	N/A
18 months	T	T	N/A
24 months	T	T	N/A
36 months	TM	TM	N/A

T = Full Analysis, **M** = Microbiological test **N/A** = Not Applicable (no storage/testing performed)

Analytical procedure applied
The shelf-life specifications and associated analytical methods are as described in Section 3.2.P.5.1.

Conclusion
Microlax, packaged in 5 mL in white LDPE plastic tubes, is stable over the 36 months period of observation for batches 0602072, 0606458 and 0606459 with no adverse trend or excursions

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2.3.P.8.2 Post-approval Stability Protocol and Stability Commitment

The company commits to place a minimum of one full commercial scale batch under on stability, under on-going conditions, provided the product is manufactured in that year.
The product will be analysed according to the tests and specifications described in section 3.2.P.5.1.

2.3.P.8 STABILITY

2.3.P.8.1 Stability Summary and Conclusion

2.3.P.8.1.1 Stability on batches manufactured in Famar Orléans

Batches 0602072, 0606458 and 0606459 have been followed in stability in compliance with ICH conditions.

Batch Nr	Batch 0602072	Batch 0606458	Batch 0606459
Batch size	3000 L		
Packaging	5 mL white LDPE plastic tubes		
Manufacturing site	Famar Orléans (Orléans, France)		
Use of batch	Stability study Commercial use		
Manufacturing date	April 2006	December 2006	December 2006
Initial date	May 2006	December 2006	December 2006

Details of the stability protocol for batches 0602072, 0606458 and 0606459 are outlined in the table below.

Periods	Conditions of Storage		
	25°C/60%RH	**30°C/65%RH**	**40°C/25%RH**
Initial	TM	TM	TM
3 months	T	T	T
6 months	T	T	T
9 months	T	T	N/A
12 months	T	T	N/A
18 months	T	T	N/A
24 months	T	T	N/A
36 months	TM	TM	N/A

T = Full Analysis, **M** = Microbiological test **N/A** = Not Applicable (no storage/testing performed)

Analytical procedure applied

The shelf-life specifications and associated analytical methods are as described in Sections 3.2.P.5.1.and 3.2.P.5.2 respectively.

Water loss studies

As Microlax is packaged in a semi-permeable container, appropriate data has been generated to assess water loss during the shelf-life of the product.

Water loss studies have been performed on two batches (0H1774C and 0H2067A). The stability data for these two batches (LDPE white tube, LDPE white cap and LDPE white cannula) up to 3 months at long term (25 ^{0}C/40% RH) and accelerated (40 ^{0}C/25% RH) storage conditions are provided in Section 3.2.P.8.3.

The water loss after 3 months at accelerated conditions was well below 5% and consequently no further analysis was deemed necessary. The data demonstrated that the drug product can withstand low relative humidity environments.

2.3.P.8.1.2 On-going stability study:

Three batches 0A08249A, 0E5075A and 0H1583D have been undergone on-going stability data. The detailed stability data is provided in Section 3.2.P.8.3 'Stability Data'.

Batch Nr	Batch 0A08249A	Batch 0E5075A	Batch 0H1583D
Batch size	3000 L		
Packaging	5 mL white LDPE plastic tubes		
Manufacturing site	Famar Orléans (Orléans, France)		
Use of batch	Stability study Commercial use		
Initial date	February 2011	December 2013	April 2015

Conclusion

Microlax, packaged in 5 mL in white LDPE plastic tubes, is stable over the 36 months period of observation for batches 0602072, 0606458 and 0606459. There was no adverse trend or excursions from registered shelf life specification for any test parameter, at any of the storage conditions. The water loss study demonstrated that the drug product can withstand low relative humidity environments.
The on-going stability study is also being conducted. From the three batches (on-going) stability data it is found that the product is stable over 36 months.

2.3.P.8.2 Post-approval Stability Protocol and Stability Commitment

The company commits to place a minimum of one full commercial scale batch under on stability, under on-going conditions, provided the product is manufactured in that year. The product will be analysed according to the tests and specifications described in section 3.2.P.5.1.

2.3.P.8.3 Stability Data

		Batch 0602072			Batch 0606458			Batch 0606459		
Test	**Period**	**25°C/60%RH**	**30°C/65%RH**	**40°C/25%RH**	**25°C/60%RH**	**30°C/65%RH**	**40°C/25%RH**	**25°C/60%RH**	**30°C/65%RH**	**40°C/25%RH**
Appearance *A colourless, viscous solution containing small air bubbles*	Initial	Pass			Pass			Pass		
	3 months	Pass*	Pass	Pass*	Pass	Pass	Pass	Pass	Pass	Pass
	6 months	Pass	Pass*	Pass*	Pass	Pass	Pass	Pass	Pass	Pass
	9 months	Pass*	Pass*	-	Pass	Pass	-	Pass	Pass	-
	12 months	Pass*	Pass*	-	Pass	Pass	-	Pass	Pass	-
	18 months	Pass*	Pass*	-	Pass	Pass	-	Pass	Pass	-
	24 months	Pass	Pass*	-	Pass	Pass	-	Pass	Pass	-
	36 months	Pass	Pass	-	Pass	Pass	-	Pass	Pass	-
* Presence of 2 phases										
Deliverable volume *Volume not less than stated on the label(in ml)*	Initial	5.2			5.2			5.1		
Density after deaeration *1.25 to 1.31 g/ml*	Initial	1.30			1.29			1.29		
	3 months	1.28	1.29	1.29	1.29	1.29	1.30	1.29	1.29	1.30
	6 months	1.29	1.29	1.30	1.30	1.30	1.30	1.30	1.31	1.30
	9 months	1.29	1.29	-	1.29	1.29	-	1.29	1.29	-
	12 months	1.28	1.29	-	1.29	1.29	-	1.30	1.30	-
	18 months	1.29	1.29	-	1.29	1.29	-	1.29	1.29	-
	24 months	1.29	1.30	-	1.31	1.30	-	1.31	1.31	-
	36 months	1.29	1.30	-	1.30	1.30	-	1.30	1.30	-
pH *6.0 to 8.0*	Initial	6.8			6.8			6.7		
	3 months	6.7	6.7	6.8	6.8	6.8	6.8	6.8	6.8	6.8
	6 months	6.8	6.8	6.9	6.8	6.9	6.9	6.9	6.9	6.9
	9 months	6.8	6.8	-	6.8	6.8	-	6.8	6.8	-
	12 months	6.9	6.9	-	6.8	6.8	-	6.8	6.8	-
	18 months	6.8	6.8	-	6.8	6.8	-	6.8	6.9	-
	24 months	6.9	6.8	-	6.8	6.8	-	6.8	6.8	-
	36 months	6.9	6.8	-	6.9	6.9	-	6.9	6.9	-

		Batch 0602072			Batch 0606458			Batch 0606459		
Test	**Period**	**25°C/60%RH**	**30°C/65%RH**	**40°C/25%RH**	**25°C/60%RH**	**30°C/65%RH**	**40°C/25%RH**	**25°C/60%RH**	**30°C/65%RH**	**40°C/25%RH**
Sodium lauryl sulphoacetate id. *Positive colour reaction*	Initial	Pass			Pass			Pass		
Sodium citrate id. *Positive colour reaction*	Initial	Pass			Pass			Pass		
Sorbitol id. *Rf value matches standard*	Initial	Pass			Pass			Pass		
Sodium lauryl sulphoacetate assay *8.5 to 9.5 mg/ml*	Initial	9.1			9.1			9.1		
	3 months	8.9	8.9	8.9	9.0	9.1	9.3	8.9	8.9	8.8
	6 months	8.8	8.8	8.8	9.3	9.2	9.0	8.9	8.9	9.1
	9 months	8.9	8.9	-	8.6	9.1	-	8.9	8.9	-
	12 months	8.7	8.8	-	8.7	8.7	-	8.9	9.1	-
	18 months	8.9	8.8	-	9.0	9.0	-	8.9	9.0	-
	24 months	9.0	9.0	-	8.3 (9.1)*	7.3 (8.5)*	-	7.8 (9.1)*	7.9 (9.1)*	-
	36 months	9.2	9.2	-	8.6	8.7	-	8.7	9.2	-
Sodium citrate assay *83 to 98 mg/ml*	Initial	93			92			90		
	3 months	92	92	93	92	92	94	92	92	94
	6 months	92	92	96	93	93	94	92	93	90
	9 months	92	93	-	92	92	-	92	92	-
	12 months	87	93	-	93	93	-	93	93	-
	18 months	92	93	-	93	93	-	93	93	-
	24 months	91	91	-	94	94	-	94	95	-
	36 months	94	95	-	94	95	-	94	94	-
Sorbitol assay *594 to 656 mg/ml*	Initial	625			641			634		
	3 months	629	620	638	632	633	636	635	625	635
	6 months	634	638	654	626	641	598	647	625	636
	9 months	607	610	-	616	622	-	620	624	-
	12 months	611	624	-	612	629	-	634	635	-
	18 months	640	639	-	638	617	-	621	634	-
	24 months	606	623	-	649 (649)*	647 (649)*	-	652 (653)*	654 (655)*	-
	36 months	643	644	-	650	652	-	646	650	-

*A new method was applied at 24 months for the assay of sorbitol (HPLC) and Sodium laurylsulfoacetate (potentiometric titration method). Some adjustments in the operating conditions were necessary to obtain a full homogenization of the analyte. Values in parenthesis represent final results were obtained at 27 months.

		Batch 0602072			Batch 0606458			Batch 0606459		
Test	**Period**	**25°C/60%RH**	**30°C/65%RH**	**40°C/25%RH**	**25°C/60%RH**	**30°C/65%RH**	**40°C/25%RH**	**25°C/60%RH**	**30°C/65%RH**	**40°C/25%RH**
Sorbic acid assay	Initial		0.95			0.98			0.99	
≥ 0.90 mg/ml	3 months	0.92	0.93	0.93	1.00	0.98	0.98	0.99	0.98	0.99
	6 months	0.95	0.96	0.97	0.98	0.97	0.97	0.98	0.98	0.97
	9 months	0.94	0.93	-	0.97	0.96	-	0.97	0.97	-
	12 months	0.92	0.92	-	0.97	0.96	-	0.97	0.96	-
	18 months	0.92	0.91	-	0.97	0.95	-	0.97	0.95	-
	24 months	0.91	0.91	-	0.98	0.95	-	0.99	0.97	-
	36 months	0.93	0.92	-	0.95	0.94	-	0.95	0.92	-
Microbiological quality *TAMC 10^3 (CFU/mL)* *TYMC 10^2 (CFU/mL)* *Escherichia coli*** *absence in 1 ml*	Initial	Pass			Pass			Pass		
	36 months	Pass	Pass	-	Pass	Pass	-	Pass	Pass	-

** In accordance with the current Ph. Eur. 5.1.4, the testing for E. Coli is not mandatory for the rectal formulations.

Water loss stability data:

Test	Period	Batch 0H1774C		Batch 0H2067A		Test Status
		25°C/40%RH	40°C/25%RH	25°C/40%RH	40°C/25%RH	
Weight loss bottle A	3 months	0.2%	1.4%	0.2%	1.4%	Pass
Weight loss bottle B	3 months	0.2%	1.4%	0.2%	1.4%	Pass
Weight loss bottle C	3 months	0.2%	1.4%	0.2%	1.4%	Pass
Weight loss bottle D	3 months	0.2%	1.4%	0.2%	1.4%	Pass
Weight loss bottle E	3 months	0.2%	1.4%	0.2%	1.4%	Pass
Weight loss bottle F	3 months	0.2%	1.4%	0.2%	1.4%	Pass

On-going stability data

Test	Period	Batch 0A08249A	Batch 0E5075A	Batch 0H1583D
Description *A colourless, viscous solution containing small air bubbles*	Initial	Pass	Pass	Pass
	12 months	Pass	Pass	Pass
	24 months	Pass	Pass	Pass
	36 months	Pass	Pass	Pass
Deliverable volume *Volume not less than stated on the label(in ml)*	Initial	Pass	Pass	Pass
	12 months	Pass	Pass	Pass
	24 months	Pass	Pass	Pass
	36 months	Pass	Pass	Pass
Density after deaeration *1.25 to 1.31 g/ml*	Initial	1.29	1.28	1.28
	12 months	1.29	1.29	1.29
	24 months	1.29	1.29	--
	36 months	1.29	1.29	--
pH *6.0 to 8.0*	Initial	6.7	6.8	6.9
	12 months	6.9	7.0	6.8
	24 months	6.8	6.8	--
	36 months	6.8	6.8	--
Sodium lauryl sulphoacetate assay *8.5 to 9.5 mg/ml*	Initial	9.0	8.9	8.9
	12 months	9.0	9.0	9.1
	24 months	9.0	8.7	--
	36 months	8.8	9.3	--
Sodium citrate assay *87 to 96 mg/ml*	Initial	92	92	92
	12 months	93	91	92
	24 months	94	94	--
	36 months	94	92	--
Sorbitol assay *594 to 656 mg/ml*	Initial	611	636 (612)*	598 (622)*
	12 months	611 (641)*	630 (635)*	646 (636)*
	24 months	624 (643)*	628 (650)*	--
	36 months	634 (640)*	630 (649)*	--
Sorbic acid assay *≥ 0.90 mg/ml*	Initial	0.97	0.99	0.92
	12 months	0.95	0.97	0.91
	24 months	0.95	0.95	--
	36 months	0.93	0.94	--

*Sorbitol assay by HPLC

Test	Period	Batch 0A08249A	Batch 0E5075A	Batch 0H1583D
Microbiological quality *TAMC NMT 2000 CFU/mL* *TYMC NMT 2000 CFU/mL*	Initial	Pass	Pass	Pass
	60 months	Pass	--	--