CBG MEB

Public Assessment Report

Scientific discussion

Clensia, powder for oral solution

(Macrogol 4000, anhydrous sodium sulphate, sodium citrate, simeticone, anhydrous citric acid, sodium chloride and potassium chloride)

NL/H/3414/001/DC

Date: 22 December 2016

This module reflects the scientific discussion for the approval of Clensia, powder for oral solution. The procedure was finalised on 22 June 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Event
ASMF	Active Substance Master File
BCF	Bio-Concentration Factor
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMR	Carcinogenic, Mutagenic and Reprotoxic
CMS	Concerned Member State
DT50	Degradation Time for 50% of a substance to be degraded under laboratory conditions
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
K_{ow}	Octanol-Water partition coefficient
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
NOEC	No Observed Effect Concentration
PBT	Persistent, Bioaccumulative and Toxic
PEC	Predicted Environmental Concentration
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TEAE	Treatment Emerging Adverse Event
TSE	Transmissible Spongiform Encephalopathy
vPvB	very Persistent and very Bioaccumulative

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Clensia, powder for oral solution from Alfa Wassermann S.p.A.

The product is indicated for bowel cleansing prior to any clinical procedures requiring a clean bowel e.g. bowel endoscopy or radiology.

Clensia is indicated for use in adults.

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

The individual 7 active substances within Clensia are established active substances which have been included in other medicinal products to obtain a laxative effect. However, these active substances have not been combined within one medicinal product. Clensia therefore concerns a new fixed dose combination product.

The concerned member states (CMS) involved in this procedure were Czech Republic, Germany, Spain, France, Italy, Poland, Portugal, Romania and the Slovak Republic.

The marketing authorisation has been granted pursuant to Article 10(b) of Directive 2001/83/EC.

The MAH gave the following argumentation for this fixed dose combination:

- Improvement of the benefit/risk assessment compared to other Macrogol-electrolyte solutions:
  - Addition of osmotic activities of Macrogol 4000, sodium sulphate, citric acid and sodium citrate results in a level of efficacy similar to the one achievable by each active substance used alone at higher doses than in combination, but associates with a better safety profile.
  - Presence of simeticone favours the foam coalescence which improves mucosal visibility.
  - Balance of the ion content of the Macrogol preparation by sodium sulphate, sodium chloride and potassium chloride, avoids ionic shifts in the bowel lumen and limits potential electrolytes imbalance.
- Simplification of therapy:
  - Administration of a low amount of solution (2 litres) with an acceptable taste and easy to be ingested, improves patient compliance.

Considering the relevant contribution of each active substance to the overall therapeutic effect has not been demonstrated, and that the active substances have alone and in combination been included in other medicinal products for bowel cleansing, the combined effects of the active substances within Clensia should be comparable to those of other Macrogol-electrolyte solutions indicated for bowel cleansing.
In support of this application the MAH has submitted one pharmacodynamic study (CRO-PK-07-196) and two clinical efficacy studies (PMF 104 BC1/08 and PMF 104 BC1/10). These are discussed in section IV Clinical aspects. The designs of the studies are considered suitable for the evaluation of this fixed dose combination.

Paediatric Investigation Plan
In 2014, the Paediatric Committee of the European Medicines Agency agreed on the submitted paediatric investigation plan with respect to Clensia (P/0051/2014). A waiver for the paediatric population was granted on the grounds that this medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

II. QUALITY ASPECTS

II.1 Introduction

Clensia is packed in 2 separate paper/polyethylene/aluminium sachets (type A and type B) as a white to almost white powder for oral solution. For a single dose 2 sachets of type A and 2 sachets of type B should be dissolved in 1 litre of water.

Sachet A (large) contains the following active substances:

Macrogol 4000	52.500 g
Sodium sulphate anhydrous	3.750 g
Simeticone	0.080 g

Sachet B (small) contains the following active substances:

Sodium citrate	1.863 g
Citric acid anhydrous	0.813 g
Sodium chloride	0.730 g
Potassium chloride	0.370 g

The excipients are acesulfame potassium (E950) and lime flavour (containing flavouring preparations, natural flavouring substance, icing sugar with maize starch, Arabic gum (E414) and maltodextrin).

II.2 Drug Substances

Macrogol 4000
The active substance Macrogol 4000 is an established active substance described in the European Pharmacopoeia (Ph.Eur.). Macrogol 4000 is a white or almost white solid with a waxy or paraffin-like appearance. It is very soluble in water and in methylene chloride, and practically insoluble in alcohol, fatty oils and mineral oils.

The CEP procedure is used for the active substance. 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 Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and with the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Sodium sulphate anhydrous
The active substance sodium sulphate anhydrous is an established active substance described in the Ph.Eur. The active substance is freely soluble in water. It is a white to almost white hygroscopic powder.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of

the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process has been described in sufficient detail. No organic solvents (class 1, 2 or 3), or heavy metal catalysts are used in the process. The substance is sieved after drying. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. with additional requirements for magnesium. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 full scaled batches stored at 25°C/60% RH (60 months) and 30°C/65% RH (12 months) and 40°C/75% RH (6 months). No changes are seen. The proposed retest period of 36 months and storage condition 'Keep in well-closed containers, in a dry place and at temperatures below 30°C' are justified. Although the stability results at accelerated conditions are within specification, no objection is being made to the stricter storage restriction of <30°C.

Sodium citrate
The active substance sodium citrate (dihydrate) is an established active substance described in the Ph.Eur. The active substance is freely soluble in water. Sodium citrate is a white or almost white fine crystal, slightly deliquescent in moist air.

The ASMF procedure is used for this active substance.

Manufacturing process
The manufacturing process has been described in sufficient detail. No organic solvents (class 1, 2 or 3), or heavy metal catalysts are used in the process. The substance is sieved after drying. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. with additional requirements for microbiological purity. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for seven full scaled batches stored at 25°C/60% RH (three batches up to 60 months, one batch 56 months, one batch 35 months, one batch 22 months and one batch 11 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). No changes were seen. The proposed retest period of 36 months and storage condition 'Keep in well-closed containers and at temperatures below 30°C' are justified. Although the stability results at accelerated conditions are within specification, no objection is being made to the stricture storage restriction of <30°C.

Simeticone
The active substance simeticone is an established active substance described in the Ph.Eur. It is a viscous, greyish-white, opalescent liquid. The active substance is practically insoluble in water. Simeticone contains 4-7% silica in line with the Ph.Eur.

The CEP procedure is used for this active substance.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and with the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Citric acid, anhydrous
The active substance citric acid anhydrous is an established active substance described in the Ph.Eur. It is a colourless crystal or white, crystalline powder. The active substance is very soluble in water. Full documentation on the active substance has been included in the dossier, i.e. no ASMF or CEP procedure is applied.

Manufacturing process
The manufacturing process consists of purification by dissolution, crystallisation and drying of citric acid anhydrous. Only water is used. No metal catalysts or other solvents are used. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. with additional requirements for microbial quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (60 months) and 30°C/65% RH (12 months), and for two full scaled batches stored at 40°C/75% RH (6 months). All parameters tested remained relatively stable at all storage conditions. The proposed retest period of 60 months is justified.

Sodium chloride
The active substance sodium chloride is an established active substance described in the Ph.Eur. Sodium chloride is a white or almost white, crystalline powder or colourless crystal or appears as white or almost white pearls. The active substance is freely soluble in water.

The CEP procedure is used for this active substance.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and with the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full scaled batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Potassium chloride
The active substance potassium chloride is an established active substance described in the Ph.Eur. It is a white or almost white, crystalline powder or colourless crystal. The active substance is freely soluble in water.

The CEP procedure is used for this active substance.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and with the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full scaled batches.

Stability of drug substance
The active substance is stable for 2 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Formulations similar to Clensia have been generally used in clinical practice for over 25 years and have been proved to be safe and effective in bowel cleansing prior to any clinical procedure requiring a clean bowel (e.g. bowel endoscopy or radiology). Their use typically required the administration of 4 litres of solution over a period of some hours. Administering large volumes of solution, even in case of good palatability, sometimes causes problems of patient's compliance with a consequent increase in the failure rates of the clinical investigation for which this type of preparation is intended.

The purpose of this new formulation is to increase the patient's compliance by reducing the colume of oral solution to be taken while maintaining an acceptable taste and providing high efficacy of bowel cleansing

Compared to existing formulations the following changes were adopted:
- The amount of Macrogol per litre was almost doubled and set to 105 g/l.
- The concentration of sodium and potassium chloride, electrolytes with osmotic action, was retained fore salt balance purposes, in respect to the existing formulations.
- Sodium citrate and anhydrous citric acid were introduced, acting as osmotic laxative with pleasant taste. The amount of these components was set based on the need to obtain a resulting osmolality of 420 – 470 mOsmol/kg.
- The relative ratio of sodium citrate/citric acid was set in order to obtain a resulting pH of the reconstituted solution of 4.8 corresponding to the pKa 2 of the citric acid.
- The sweetener acesulfame potassium was combined with the chosen flavouring agent, proved to be a suitable choice to complement the salty taste of the other components.
- Tests for the choice of the flavouring agent were carried out. Citrus flavours were considered more suitable for acid solution containing citrate. Due to the better palatability of the formulation, the lime flavour was selected as the best suitable option to mask the salty taste of the other components.

During the development, early stability studies on the product consisting in a blend of the components packaged in a single sachet, showed compatibility problems, in accelerated conditions, 40°C/75% RH. Therefore the components were blended separately and packaged into 2 separate sachets.
Based on the results in subsequent stability studies the formulation was finalised and the clinical studies were performed. The batches used in the clinical studies are of the same composition as the commercial batches. The manufacturing process is slightly different. However, given the nature of the

differences and the nature of the dosage form (solution at the time of administration) this is accepted. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process of sachet A consists of blending and filling. The manufacturing process of sachet B consists of milling, blending and filling. Process validation data on the product has been presented on two full scaled batches of each sachet. The product is manufactured using conventional manufacturing techniques. From the process validation data a relatively high variability in the contents of the sachet B components has been observed, which is also reflected in the batch release and stability data. Further optimisation studies of the sachet B blending process to ensure compliance with the release and shelf-life acceptance criteria are on-going. The MAH has committed to finalise the process optimisation studies post approval.

Control of excipients
The excipients comply with relevant Ph.Eur. monographs, except for the lime flavour. The qualitative composition of the lime flavour has been provided. The lime flavour complies with Regulation (EC) No 1334/2008. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, water content, average mass, content uniformity, identification, assay, impurities and microbial quality. The specification of the reconstituted solution includes tests for appearance, osmolality and pH. The drug product specification is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 2 full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for two full scale batches of sachets A and B stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). Furthermore, stability data has been provided for three additional full scale batches of sachets A and B manufactured according to the former process, stored at 25°C/60% RH (24-36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging.
The stability profile of sachet A was similar for the former and proposed process. Slight increases were observed in a known impurity content but remained within specification limits. All other parameters tested remained relatively stable throughout the test periods at both test conditions and within specification limits. The stability data for sachet B is also in line with the former process. Except for variable results for water content for both sachets, anyway remained within specification limits, no clear trends or changes were observed from the available stability data at long-term and intermediate storage conditions. At accelerated storage conditions after 6 months incompliance with the acceptance criterion for appearance was observed. Based on the presented stability data, the claimed shelf-life of 3 years for the product with storage condition 'Store below 30°C' is justified. Given the dosage form (powder in sachets) and the primary packaging material, the absence of photostability studies is accepted.

Stability data has been provided demonstrating that the product remains stable for 24 hours following reconstitution, when stored below 25°C and when refrigerated 2°C - 8°C.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Clensia has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

The following post-approval commitment was made:

- Process optimisation of the sachet B blending process should be performed. The MAH should submit a variation regarding an optimised blending process within three months after the end of the procedure.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

Clensia powder for oral solution is a mildly hyperosmotic colonic lavage solution.
The primary mechanism of action of this product is the osmotic action of macrogol 4,000 (polyethylene glycol), sodium sulphate and the citrates which cause water to be retained in the colon. This enhances rapid transportation of the solid faecal material, induces a marked laxative effect leading to colon cleansing.
Simeticone has an anti-foam activity, due to its ability to collapse bubbles by forming a thin layer on their surface, which is intended to improve mucosal visibility during colonic examination.
Acesulfame K (E950), a sweetener used in foods and beverages, is used in this product. The Acceptable Daily Intake (ADI) of acesulfame K as a sweetener for foods is 9 mg/kg bw [Scientific Committee on Food Opinion, SCF/CS/ADD/EDUL/194 final, 2000]. The maximum therapeutic dose of 2 litres Clensia leads to a maximum intake of 260 mg Acesulfame K, corresponding with a maximum dose of 4.3 mg/kg bw for a person of 60 kg. With this dose, the ADI of 9 mg/kg bw is not exceeded.
The MAH did not conduct any *in-vitro* or *in-vivo* preclinical study with Clensia, according to guidelines CPMP/SWP/799/95 (Guideline On The Non-Clinical Documentation For Mixed Marketing Authorisation Applications) and EMEA/CHMP/SWP/258498/2005 (Guideline On The Non-Clinical Development Of Fixed Combinations Of Medicinal Products).

The non-clinical overview is adequate, providing an overview of available information on pharmacology, pharmacokinetics and toxicology of the active substances. Additional non-clinical studies are not needed since all the active substances were already tested for safety and efficacy, alone or in combination in similar already marketed products.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The final product contains 7 active substances. The active substances sodium sulphate, sodium citrate, citric acid, sodium chloride and potassium chloride are considered to be electrolytes. Due to their nature, they are unlikely to result in a significant risk to the environment. Therefore, sodium sulphate, sodium citrate, citric acid, sodium chloride and potassium chloride are not expected to pose a risk to the environment.

The active substance Macrogol 4000 is also present in Colofort powder for oral solution in sachet, which has already been marketed in the Netherlands since 1999 by IPSEN Farmaceutica B.V. (RVG License Number 22626) for the same indication as Clensia. No increase in use of Macrogol 4000 is expected due to the marketing of Clensia for the same indications. An ERA is not considered necessary.

The active substance simeticone is new with respect to this indication. The MAH submitted an ERA report for simeticone.

Table 1 Summary of main study results for simeticone

Substance (INN/Invented Name): simeticone			
CAS-number: 8050-81-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	RP-HPLC	Log K_{ow} >9	Potential PBT
PBT-assessment			

Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log K_{ow}	>9	
	BCF	literature review shows that due to size (chain length 20-400 oligomers, Mw >1500 Da) of the dimethyl siloxane polymer in this active substance, uptake and hence bioaccumulation and biomagnification are unlikely to occur.	not B
Persistence	ready biodegradability	not investigated	
	DT50, parent	not investigated	
Toxicity	NOEC algae NOEC crustaceans NOEC fish	not investigated	
	CMR	not investigated	
PBT-statement :	simeticone is considered to be not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (prevalence)	0.00013	µg/l	<0.01 threshold
Other concerns (e.g. chemical class)			N

Conclusions on ERA
$PEC_{surfacewater}$ for simeticone is 0.00013 µg/l, which is below the action limit of 0.01 µg/l. Simeticone is not a PBT substance.

Considering the above data, none of the active substances are expected to pose a risk to the environment.

III.3 Discussion on the non-clinical aspects

This product is a fixed-dose formulation of established active substances. 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

The 7 active substances are well-known and have an established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. In addition, the MAH submitted a pharmacodynamic study (CRO-PK-07-196) and 2 clinical efficacy studies (PMF 104 BC1/08 and PMF 104 BC1/10), which are discussed below.

IV.2 Pharmacokinetics

Macrogol 4000, sodium sulphate and simeticone are not or minimally systemically absorbed as shown extensively in literature.

The urinary excretion of citrate was evaluated in the pharmacodynamic study (see section IV.3 for further description). The evaluation showed that urinary excretion of citrate acid did not correlate with the administered dose of Clensia. Furthermore it was shown that urinary excretion of citrate acid after

administration of Clensia was comparable to citrate acid excretion after administration of a reference which does not contain citrate acid. These results indicate that citrate absorption is low.

IV.3 Pharmacodynamics

Mechanism of action
The (postulated) mechanisms of action of the active substances within Clensia have been provided:

Macrogol
Macrogol (polyethylene glycol (PEG)) is administered in a dilute electrolyte solution. As a result of the osmotic effect of Macrogol, the electrolyte solution is retained in the colon, where it works as bowel cleanser. Due to the electrolytes there is little fluid exchange across the colonic mucosal membrane. Hence, the possibility of systemic electrolyte disturbance and fluid disturbances is rather low.

Sodium sulphate, sodium chloride and potassium chloride
Sodium sulphate contributes to the laxative effect creating an electrochemical gradient for fluid transport, as the sulphate anion is poorly absorbed, and osmotically active sulphate salts (and water) are therefore retained in the lumen.
Sodium sulphate, sodium chloride and potassium chloride, balance the ion content of the Macrogol preparation, in order to avoid ionic shifts in the bowel lumen and to limit potential electrolytes imbalance.

Citric acid and sodium citrate
Citric acid is a non-toxic substance that increases the overall cathartic effect, in terms of amount of produced faeces (increased stool volume), and improves the palatability and ease of ingestion, and therefore the overall patient acceptance. Citric acid is naturally present in the body and is a common ingredient of a normal diet. Citric acid and sodium citrate have been widely used as laxative and acidifying agents; they are also used as flavour enhancers.

Simeticone
Simeticone is included in the formula for its antifoaming properties: it does not reduce or prevent the formation of gas in the digestive tract, but decreases the surface tension of gas bubbles, promoting their coalescence and improving mucosal visibility (Wu et al., 2011; Park et al., 2009; Lazzaroni et al., 1993; McNally et al., 1988). It is not systemically absorbed.

Conclusion
The mechanisms of action of the individual active substances within Clensia have been adequately described. Other Macrogol-electrolyte solutions have been registered within the European Union. Based on these facts the fixed combination in one product is pharmacologically plausible and is based on valid therapeutic principles.

Due to the use of higher doses of Macrogol and electrolytes, Clensia is hyperosmotic compared to other Macrogol-electrolyte solutions used for bowel cleansing. Because of this and the presence of simeticone in the product, the overall amount of liquids that needs to be drunk to obtain appropriate bowel cleansing is postulated to be reduced. In addition, according to the MAH the taste of Clensia is better compared to other Macrogol-electrolyte solutions. Hence, the MAH has indicated the rationale for the fixed combination of active substances in Clensia. This is in line with the draft EMA Guideline on clinical development of fixed combination medicinal products (2015).
The intended population has been clearly identified. Other Macrogol-electrolyte solutions containing similar electrolytes (e.g. Moviprep powder for oral solution (UK/H/0891/001)) have been indicated for a similar population as proposed for Clensia.

Pharmacodynamic study CRO-PK-07-196
The MAH needed to demonstrate that the combined pharmacodynamic effects of Clensia are non-inferior to those of other Macrogol-electrolyte solutions indicated for bowel cleansing.

A study has been conducted in which the effect of Clensia at different doses on stool output is determined in comparison to SELG 1000, iso-osmotic polyethylene glycol electrolyte bowel lavage oral solution (Alfa Wassermann S.p.A., Italy), in healthy volunteers. This is considered suitable for the evaluation of this fixed dose combination.

Test and reference product
Both test and reference treatment contain Macrogol 4000, sodium sulphate anhydrous, sodium chloride and potassium chloride as active substances. Sodium citrate dehydrate, citric acid anhydrous and simeticone were only included in the test product, while sodium bicarbonate was only included in the reference product.

Methods
The study concerned a single-centre, single-dose, randomised, observer-blind, cross-over pharmacodynamic study. Adults aged 18-64 years with a body mass index above 18 but below 30 kg/m^2 and no clinically relevant abnormal vital signs (blood pressure, heart rate) were eligible for inclusion.

The pilot phase consisted of 3 periods of 2 days. In the first treatment period the effects of different doses of test treatment were determined in parallel treatment groups. In the following 2 treatment periods, patients received test and reference treatment according to a cross-over design. The aim of the pilot phase was to obtain a dose-response curve with 3 different doses of the test medication (T1, T2, T3), to verify the variability of the efficacy parameters and to compare in an exploratory way the pharmacodynamics of the highest dose of the test (T3) vs. the reference treatment. Eight subjects were included in this pilot study phase.
The pivotal study phase consisted of 2 periods of 2 days. Included subjects in this study phase (n=28) received both test (T3) and reference treatment according to a cross-over design. The objective of the pivotal study was to compare the pharmacodynamics of the test formulation T3 vs. the reference formulation administered to healthy male and female volunteers under fasting conditions according to a randomised cross-over design.

During each study period the subjects were confined from the evening preceding the drug administration (study day 0), up to the evening of day 1. Study treatment was administered at once in the morning of day 1. All subjects drank 250 ml of mineral water at 6 and 9 hours post-dosing. Patients who had received test treatment drank 0.5, 0.75, and 1 litre of additional water after administration of T1, T2, and T3 respectively. Subjects did not take any food or drink for about 24 hours, from the evening of day 0 until leaving the clinical centre on day 1, after 12 hour post-dose. During confinement, routine ambulant daily activities were recommended, but hazardous, strenuous or athletic activity was not permitted. There was a period of at least 7 days between 2 consecutive administrations of study treatment.
Only the principal investigator recording the occurrence of adverse events (AEs) and performing the clinical assessments was under blind conditions and therefore unaware of the administered treatment.

Endpoints and analyses
Primary endpoint was to demonstrate the non inferiority of T3 *vs*. reference in terms of absolute and normalised stool weight after single dose administration of study treatment (pivotal phase). Normalised stool weight concerns the absolute stool weight adjusted for (i.e. divided by) the amount of fluid administered together with the study medication. This weight is expected to increase upon higher administered doses of Macrogol-electrolyte solution.
Key secondary endpoints in the pilot and pivotal study phase included: the dose-response curve of the 3 test treatments (T1, T2, T3) in terms of absolute and dose-normalised stool weight; absolute and normalised stool weight after reference administration; urinary excretion of creatinine-corrected citric acid after administration of the 3 test treatments (T1, T2 and T3) vs. baseline (see chapter IV.2), body weight prior to administration of study treatment and 12 hour post-dosing, safety and tolerability of the study treatments (i.e. AEs, vital signs [blood pressure, heart rate], ECG, laboratory parameters, easiness/difficulty to drink, and palatability of the study products).

Primary analysis in the pivotal study phase concerned the comparison of cathartic effects of test and reference treatment in terms of absolute stool weight normalised for the weight of total liquid intake. This normalised stool weight was calculated by dividing the total stool weight (g) 0-12 hours after administration by the total weight (g) of medication-water administered during that period.
A non-inferiority margin of 20% of the normalised stool weight obtained for the reference treatment was applied with respect to the mean difference in normalised stool weight between test and reference treatment. The MAH has not justified the chosen non-inferiority margin of 20% of the normalised stool weight for the reference treatment with respect to the mean difference in normalised stool weight

between test and reference treatment. As the study was mainly designed to demonstrate pharmacodynamic effects of Clensia, the lack of such a justification is not considered of crucial importance.

The allowed food intake and physical activity during confinement are appropriate to investigate the effects of study treatment. The restriction of food intake to clear fluids is necessary to obtain appropriate bowel cleansing apart from effects of study treatment.
Determination of stool weight is an appropriate pharmacodynamic endpoint with respect to Macrogol-electrolyte solutions. Due to osmotic effects of these solutions the amount of water in the gastro-intestinal tract is expected to increase. The electrolytes within the Macrogol-electrolyte solution promote gastro-intestinal passage, thereby limiting fluid reuptake. Due to the effects of Macrogol-electrolyte solutions, the amount of water in the stools will increase and therewith also stool weight. An increased stool weight therefore supports postulated pharmacodynamic effects of Macrogol-electrolyte solutions.

Urinary volume and weight are not directly relevant with respect to bowel cleansing. For this reason, respective outcomes are not discussed with respect to pharmacodynamics.

Results
Fifty-five subjects were screened and 42 of them were randomised and received study treatment. Nine of them were randomised to take part in the pilot phase, while the other 33 were randomised to take part in the pivotal phase. One subject discontinued study treatment in the pilot study phase, and 5 subjects discontinued study treatment in the pivotal study phase. Of this total of 6 subjects, 3 subjects withdrew consent for personal reasons and 3 subjects left the study due to AEs. Thirty-six of the randomised subjects completed the study per protocol (table 2).

Table 2. Weight of body, stools, medication-water and normalised stool weight in pilot study phase and pivotal study phase.

	Reference treatment	Test treatment		
	4 bags /4 litre of water	T1 (2 bags / 1 litre of water)	T2 (3 bags/ 1.5 litre of water)	T3 (4 bags/ 2 litres of water)
Pilot study phase	n= 8	n= 4	n= 5	n= 8
Body weight (kg), mean Pre-dose 12h post dose Difference p-value	 81.84 (14.7) 81.18 (14.3) -0.66 0.006	 88.13 (5.0) 87.72 (4.7) -0.41 0.10	 78.29 (17.3) 77.58 (17.1) -0.71 0.02	 81.22 (14.5) 80.65 (14.4) -0.57 < 0.001
Total stool weight (g) 0-12 h after administration, mean (SD)	3750.4 (375.0)	1246.5 (213.3)	2000.9 (169.7)	2841.8 (325.6)
Total weight of medication-water administered (g), mean (SD)	4527.1 (6.7)	2008.4 (1.5)	2762.9 (4.8)	3524.5 (5.4)
Normalised total stool weight 0-12 h after administration, mean (SD)	0.83 (0.08)	0.62 (0.11)	0.72 (0.06)	0.81 (0.09)
Mean difference in normalised total stool weight between reference treatment and dose T3 of test treatment (95% CI)	0.02 (-0.07 - 0.11)	--	--	--
Pivotal study phase	n= 28	n= 0	n= 0	n= 28
Total stool weight (g) 0-12 h after administration, mean (SD)	3726.4 (296.2)	--	--	2594.6 (292.6)
Total weight of medication-water administered (g), mean (SD)	4524.9 (3.3)	--	--	3531.5 (10.2)
Normalised total stool weight 0-12h after administration, mean (SD)	0.82 (0.07)	--	--	0.73 (0.08)
Mean difference in normalised total stool weight between reference treatment and dose T3 of test treatment (95% CI)	0.09 (0.05 - 0.13)	--	--	--
Time (h) between first study drug administration and the last elimination of stool residuals, mean (SD)	3.4 (1.6)	--	--	4.9 (3.1)
Product palatability (%): Very unpleasant Unpleasant Acceptable Good	 3.5 6.9 37.9 48.3	--	--	 0 39.4 33.3 27.3

Very good	3.5			0
Product acceptance (%):				
Difficult	13.8	--	--	39.4
Acceptable	62.1			33.3
Easy	24.1			27.3

In the pilot study phase, body weight decreased by 0.4 up to 0.7 kg upon administration of test and reference treatment. For most study treatments, differences compared to baseline were statistically significant (p≤ 0.02). This however does not apply to T1 (2 bags of study treatment dissolved in one litre of water; p= 0.10). Normalised total stool weight 0-12 hours after administration was 0.83 (95% CI: 0.76–0.90) for the reference treatment. A non-inferiority margin of 20% of this normalised stool weight (0.17) was chosen. For the test treatment, respective normalised total stool weight increased with increasing doses of test treatment (0.62 up to 0.81 for T1-T3). Mean (95% CI) difference in normalised cumulative stool weight between reference treatment and dose T3 of test treatment was 0.02 (95% CI: -0.07-0.11). Both limits of respective confidence interval (CI) are above the chosen non-inferiority margin of -0.17. Hence, test treatment was non-inferior to reference treatment with respect to normalised stool weight.

In the pivotal study phase, normalised total stool weight 0-12 hours after administration was 0.73 (95% CI: 0.70-0.77) for dose T3 of the test treatment and 0.82 (95% CI: 0.80–0.85) for the reference treatment. A non-inferiority margin of 20% of the mean of the normalised total stool weight of the reference treatment, 0.16, was chosen. The mean difference of normalised cumulative stool weight for reference treatment minus dose T3 of test treatment was 0.09 with 95% CI ranging from 0.05 up to 0.13. Both limits of respective CI are above the chosen non-inferiority margin of -0.16. Hence, like in the pilot study phase, the test treatment was non-inferior to the reference treatment with respect to normalised stool weight.

Palatability of study treatment was acceptable to very good in 60.6% of patients who had received dose T3 of test treatment and 89.7% of patients who had received reference treatment. Product administration was acceptable to easy according to 60.6% of patients who received dose T3 of test treatment and 86.2% of patients who received reference treatment.

Conclusion
Above results show that the normalised total stool weight 0-12 hours post dosing for dose T3 of test treatment Clensia was comparable to that of reference treatment SELG 1000. This indicates that pharmacodynamic effects of both products are similar.

Overall product palatability and product acceptance of Clensia were lower compared to reference treatment SELG 1000 in pharmacodynamic study CRO-PK-07-196. Opposite results were obtained in clinical study PMF 104 BC1/08 (see below). The MAH sufficiently explained that differences in patient's acceptability between pharmacodynamic study CRO-PK-07-196 and phase 3 study PMF 104 BC1/08 may be based on a faster intake of study treatment in the pharmacodynamic study. This explanation is acceptable.

IV.4 Clinical efficacy

Two clinical efficacy studies
Two randomised, parallel group, observer-blind, active-controlled studies have been conducted to determine the efficacy of Clensia compared to the reference treatments SELG 1000 (Study PMF 104 BC1/08) and Moviprep powder for oral solution (Study PMF 104 BC1/10) in terms of bowel cleansing prior to colonoscopy.

Reference products
SELG 1000 is an iso-osmotic polyethylene glycol electrolyte bowel lavage oral solution authorised by Promefarm S.r.l. in Italy. Both Clensia and SELG 1000 treatment contain Macrogol 4000, sodium sulphate anhydrous, sodium chloride and potassium chloride as active substances. Sodium citrate dehydrate, citric acid anhydrous and simeticone are only included in Clensia, while sodium bicarbonate is only included in SELG 1000.

Moviprep concerns a fixed dose application which has been authorised in the Netherlands by Norgine B.V. since 15 January 2007 through mutual recognition procedure UK/H/0891/001. Both Clensia and

Moviprep contain Macrogol (Clensia: Macrogol 4000; Moviprep: Macrogol 3350), sodium sulphate, sodium chloride and potassium chloride as active substances. Sodium citrate dehydrate, citric acid anhydrous and simeticone are only included in Clensia, while ascorbic acid, and sodium ascorbate are only included in Moviprep.

Methods
In both studies, out-patients aged 18 up to 85 years undergoing colonoscopy for various reasons were eligible for inclusion. Main exclusion criteria were: known or suspected gastrointestinal obstruction or perforation, toxic megacolon, major colonic resection, and other relevant diseases that could interfere with the aim of the study.

In study PMF 104 BC1/08, study patients were randomised to Clensia or SELG 1000. In study PMF 104 BC1/10, study patients were randomised to Clensia or Moviprep. Four bags of powder for oral solution were dissolved in 2 (Clensia/Moviprep) or 4 litres (SELG 1000) of dissolution water. If colonoscopy was scheduled before 12 a.m., the full dose of study treatment was administered on the day before the colonoscopy. If colonoscopy was scheduled after 12 p.m., half of the treatment dose and half of the required amount of clear fluids were administered on the day before colonoscopy. The other half of these solutions and fluids were administered in the morning of the day of colonoscopy. Colonoscopies were conducted by endoscopists who were unaware of the assigned study treatment.

In both studies, low residue diet was prescribed for 3 days before colonoscopy. During and after bowel preparation with study treatment, solid food was not allowed. Only clear liquid could be taken until colonoscopy. There were no restrictions about either previous or concomitant treatments.

Endpoints and analyses
Primary endpoint was to demonstrate the equivalence of Clensia to SELG 1000 and Clensia to Moviprep in PMF 104 BC1/08 and PMF 104 BC1/10 studies respectively, by the proportion of patients with excellent or good bowel cleansing determined with the validated Ottawa bowel preparation scale (Rostom and Jolicoeur, 2004). Secondary endpoints included: overall visibility of the mucosa (optimum, adequate, insufficient), caecal intubation (completeness of the exam), time to complete the exam (min), safety, tolerability, compliance with preparation, product acceptance (no/mild/moderate/severe distress), and willingness (yes/no) to repeat study treatment with respect to future exams.

The colon cleansing total score (primary variable) was calculated as the sum of the colon cleansing scores of each section of the colon and the overall colonic fluid score.

Equivalence testing was conducted considering the proportion of study patients with a successful colon cleansing, i.e. the proportion of subjects with a colon cleansing total score rated as excellent or good (≤6). The null hypothesis was tested by constructing the two-sided 95% CI for the difference in the success rate (p clinically successful, test - p clinically successful, reference) assuming a success rate of bowel cleansing (good to excellent) of 0.75. The MAH substantiated this success rate by stating that most success rates of bowel cleansing upon application of the Ottawa Bowel Cleansing Score vary between 70% and 90%.

The lower limit of the CI was compared with the lower equivalence margin of -15% and the upper limit of the CI was compared with the upper equivalence margin of 15%. Such a margin has been used before in studies investigating the effects of bowel cleansing (Bitoun et al., 2006).

Results
421 Patients were included in Study PMF 104 BC1/08 and 389 patients were included in Study PMF 104 BC1/10. About half of included patients were men (45-51% respectively). Mean age was above 55 years of age. Patients up to 83 years of age have been included.

Study outcomes of Study PMF 104 BC1/08 and Study PMF 104 BC1/10 in the intention-to-treat population are presented in Table 3. In Study PMF 104 BC1/08, 421 patients have received study treatment. Of these, 213 patients received test treatment, and 208 patients received reference treatment. In Study PMF 104 BC1/10, 385 patients have received study treatment. Of these, 193 patients received test treatment, and 192 patients received reference treatment.

In both clinical studies, good to excellent bowel cleansing scores was obtained in over 65% of patients. In additional analyses, the MAH demonstrated that bowel cleansing in the right colon, mid colon and rectosigmoid colon were comparable for test and reference treatment.

The 95% CI with respect to differences in success rate between test and reference treatment were in between the predefined equivalence margins. Hence, in both studies test and reference treatment are considered therapeutically equivalent.
In both studies, bowel cleansing success rate tended to be higher in the split dose regiment compared to the full dose regimen.

In the intention-to-treat population of Study PMF 104 BC1/08, fewer patients on test treatment experienced distress upon taking study treatment compared to patients on reference treatment (27.2% vs. 37.0%; p= 0.03). In line with this, a larger proportion of patients on test treatment was willing to repeat the intake compared to patients who had received reference treatment (93.9% vs. 82.2%; p= 0.0002).

By contrast, in Study PMF 104 BC1/10, distress upon intake of study treatment tended to occur more often upon intake of test treatment compared to reference treatment (54.6% vs. 49.7%). Respective difference was however not statistically significant (p= 0.74). The proportion of patients who were willing to repeat study treatment was similar for test and reference treatment (90.2% vs. 90.7% respectively; p= 0.88).

In additional analyses, it was observed that the proportion of patients experiencing no distress upon administration of study treatment was higher upon split dosing compared to administration of study treatment at once (Clensia: 84.4% vs. 69.6%; SELG 1000: 69.6% vs. 61.1%) in study PMF 104 BC1/08. By contrast, in study PMF 104 BC1/10 the proportion of patients experiencing no distress upon administration of study treatment was lower upon split dosing compared to administration of study treatment at once (Clensia: 35.8% vs. 51.2%; Moviprep: 50.0% vs. 50.4%).

Table 3. Study outcomes of Study PMF 104 BC1/08 and Study PMF 104 BC1/10 (intention-to-treat population)

	Study PMF 104 BC1/08			Study PMF 104 BC1/10		
	Test treatment Clensia	Reference treatment SELG 1000	Total	Test treatment Clensia	Reference treatment Moviprep	Total
Intention to treat	**n= 213**	**n= 208**	**n= 421**	**n= 193**	**n= 192**	**n= 385**
Bowel cleansing (%)						
Excellent	37.6	37.0	37.3	52.3	49.0	50.7
Good	30.5	32.2	31.4	26.4	25.5	26.0
Poor	21.6	24.5	23.0	16.6	22.4	19.5
Inadequate	10.3	6.3	8.3	4.7	3.1	3.9
Successful (%)	68.1	69.2	68.6	78.8	74.5	76.6
Failure (%)	31.9	30.8	31.4	21.2	25.5	23.4
Mean difference in success rate (% (95% CI))	-1.16 (-10.02 - 7.71)		--	4.28 (-13 - 4)		--
Full dose (n)	168	162	330	129	132	261
Successful (%)	63.1	65.4	64.2	75.0	72.5	73.8
Failure (%)	36.9	34.6	35.8	25.0	27.5	26.2
Split dose (n)	45	46	91	67	61	128
Successful (%)	86.7	82.6	84.6	86.2	78.7	82.5
Failure (%)	13.3	17.4	15.4	13.8	21.3	17.5
Colonic imaging (%)						
Optimum	60.1	54.8	57.5	53.9	50.5	52.2
Adequate	34.7	41.3	38.0	38.8	40.6	39.7
Insufficient	5.2	3.8	4.5	7.3	8.9	8.1
Caecal intubation (%)	92.0	94.7	93.3	94.8	96.4	95.6
Time to reach the caecum (min), mean (SD)	10.5 (7.1)	10.9 (7.3)	10.7 (7.2)	8.9 (7.0)	9.1 (6.2)	9.0 (6.6)
Withdrawal time (min), mean (SD)	11.6 (6.6)	12.4 (7.8)	12.0 (7.2)	11.2 (6.7)	12.7 (8.2)	12.0 (7.6)
Ease of taking the preparation (%)						
No distress	72.8	63.0	67.9	46.4	50.3	48.3
Mild distress	20.7	24.0	22.3	35.1	30.6	32.8
Moderate distress	6.6	13.0	9.7	16.0	15.5	15.8
Severe distress	0	0	0	2.6	3.6	3.1
Willingness to repeat the intake (%)						
Yes	93.9	82.2	88.1	90.2	90.7	90.4
No	6.1	17.8	11.9	9.8	9.3	9.6

Effects of Clensia with respect to bowel cleansing, mucosal visibility, and ease of taking the preparation were comparable for male and female study patients in both clinical studies. Bowel cleansing was lowest in patients aged ≥75 years for Clensia, SELG 1000, and Moviprep, i.e. for all treatments.

In additional analyses the MAH demonstrated that patients' acceptability of the product was comparable for administration of the product in a single dose or in two split doses.

The use of simeticone

The MAH substantiated the use of simeticone within the fixed combination product. The MAH indicated that in the two conducted studies (PMF 104 BC1/08 and PMF 104 BC1/10) mucosal visibility tended to be higher (3-5%) in favour of Clensia compared to reference products without simeticone, but did not reach the statistical significance. As mucosal visibility concerned a secondary endpoint in these studies, power calculations in these studies were not based on this endpoint.

To support its study results, the MAH also referred to a meta-analysis of Wu (2011). In this meta-analysis, simeticone within Macrogol-electrolyte solutions was found to reduce the amount of bubbles (odds ratio 39.3; 95% CI 11.4 – 135.9).

Circumferential evidence (e.g. from treatment guidelines, registered medicinal products) substantiates that simeticone is used in clinical practice because of its effects to increase mucosal visibility. Treatment guidelines of both the American Society for Gastrointestinal Endoscopy and the European Society of Gastrointestinal Endoscopy indicate that simeticone may - at least in some circumstances-

be added to a standard bowel preparation to increase mucosal visibility (Hassan et al., 2013). In Italy, simeticone has been included in a registered Macrogol-electrolyte solution for bowel cleansing (Selg-Esse). Hence, simeticone appears to be used in clinical practice because of its effects to increase mucosal visibility.

Although some uncertainty remains on the additive effects on improving detection of pathological findings, simeticone is a well known substance effective in reducing the number of bubbles. The MAH referred to data from literature supporting an enhanced mucosal visibility upon addition of simeticone to a standard bowel preparation (Tongprasert et al., 2009), which is also included in the meta-analysis of Wu (Wu et al., 2011). It is reasonable to assume that this will decrease the number of antifoaming interventions during colonoscopy and decrease colonoscopy time. The addition of simeticone might also increase the chance to detect pathological findings due to an improved mucosal visibility. No safety issues were associated with the use of simeticone.

Overall it is concluded that it is acceptable to add simeticone to Macrogol-electrolyte solutions to improve mucosal visibility.

IV.5 Clinical safety

Treatment-emergent adverse events (TEAEs)
An overview of recorded TEAEs in the three conducted studies in humans is presented in Table 4. Overall, 89 AEs occurred during the course of the studies. The most frequent symptom was nausea with an incidence of 15% in each treatment group, followed by bloating and abdominal pain/cramps (10% in Clensia vs. 12% comparators), and anal irritation (7% in Clensia vs.13% comparators).
TEAEs, defined as AEs that started on or after dose administration, occurred in the same proportion of Clensia and comparators-treated subjects (10% vs. 8.4%) during the study periods. The majority of AEs in studies CRO-PK-07-196 and PMF 104BC1/08 were mild.

The occurrence of treatment-related TEAEs was overall comparable for Clensia and comparative treatment (9.8% vs. 8.2%). TEAEs tended to occur more frequently upon Clensia compared to SELG 1000 in the pharmacodynamic study (10 vs. 2 subjects). In clinical study PMF 104 BC/108, the occurrence of related TEAEs was however comparable for Clensia and SELG 1000.

Table 4. Overview of AEs in individual and pooled studies.

	Pooled trials		**Study CRO-PK-07-196**		**Study PMF 104 BC1/08**		**Study Study PMF 104 BC1/10**	
	Clensia	Comparators	Clensia	SELG 1000	Clensia	SELG 1000	Clensia	Moviprep
Number of analysed subjects (n)	451	439	42	37	213	209	196	193
Proportion of patients with at least one TEAE (%)	10	8.4	23.8	5.4	8.0	7.7	9.2	9.8
Proportion of subjects with AE leading to discontinuation (%)	0.9	0.5	7.1	2.7	0	0	0.5	0.5
Number of AEs (n)	48	41	11	2	17	17	20	22
Mild (n(%))	ns	ns	7 (21.2)	1 (3.4)	12 (5.6)	14 (6.7)	ns	ns
Moderate (n(%))	ns	ns	3 (9.1)	1 (3.4)	3 (1.4)	2 (1.0)	ns	ns
Severe (n(%))	ns	ns	0	0	2 (0.9)	0	ns	ns
Not assessed (n(%))	--	--	--	--	--	1 (0.5)	--	--
Related TEAEs (n(%))	44 (9.8%)	36 (8.2%)	10	2	16	15	18	19
Definite (n)	1	7	0	0	0	1	1	6
Probable (n)	24	9	10	1	8	3	6	5
Possible (n)	18	17	0	0	8	9	10	8
Unlikely (n)	1	3	0	1	0	2	1	0
Unrelated (n)	4	5	1	0	1	2	2	3

Treatment-emergent AEs by system organ class
An overview of treatment-emergent AEs is presented in Table 5.
Headache was the most commonly reported TEAE overall across treatment groups (Clensia 5.3%, comparators 2.5%). Vomiting was the second most commonly reported TEAE overall across treatment groups (Clensia 2.9% vs. comparators 1.8%). Other notably reported TEAEs were chills (Clensia

0.2%, comparators 0.9%), blood potassium decreased (Clensia 0.7%, comparators 0.5%), glossodynia (Clensia 0%, comparators 0.5%) and hot flush (Clensia 0%, comparators 0.5%).

Table 5. TEAEs by system organ class in pooled studies

System Organ Class/ Preferred Term	PMF 104 (N=451) n (%)	Comparators (N=439) n (%)
Ear and labyrinth disorders		
Vertigo	1 (0.2)	0
Eye disorders		
Dry eye	0	1 (0.2)
Eye irritation	0	1 (0.2)
Gastrointestinal Disorders		
Abdominal pain upper	1 (0.2)	1 (0.2)
Disgeusia	1 (0.2)	0
Dry mouth	1 (0.2)	0
Dyspepsia	0	1 (0.2)
Eructation	0	1 (0.2)
Glossodynia	0	2 (0.5)
Hypoesthesia oral	1 (0.2)	0
Oral discomfort	0	1 (0.2)
Vomiting	13 (2.9)	8 (1.8)
General disorders and administration site conditions		
Chills	1 (0.2)	4 (0.9)
Pyrexia	0	1 (0.2)
Infections and infestations		
Rhinitis	0	1 (0.2)
Injury, poisoning and procedural complications		
Brain contusion	0	1 (0.2)
Investigations		
Blood potassium decreased	3 (0.7)	
Metabolism and nutrition disorders		
Hypokaliaemia		2 (0.5)
Nervous system disorders		
Presyncope	1 (0.2)	0
Headache	24 (5.3)	11 (2.5)
Skin and subcutaneous tissue disorders		
Rash	0	1 (0.2)
Swelling face	0	1 (0.2)
Vascular disorders		
Hot flush	0	2 (0.5)
Hypertensive crisis	1 (0.2)	
Hypertension		1 (0.2)

PMF 104= Clensia, Comparative treatment concerns SELG 1000 and Moviprep

Forty-two out of 48 AEs (87.5%) in the Clensia treated-groups and 32 out of 41 AEs (75.6%) in the comparator-treated groups were considered to be related to the study medications (See Table 6).

The most frequently TEAEs considered drug-related by investigators were headache (Clensia 5.1%, comparators 2.5%), vomiting (Clensia 2.4%, comparators 1.4%), chills (Clensia 0.2%, comparators 0.9%), blood potassium decreased (Clensia 0.7%, comparators 0.2%) and glossodynia (Clensia 0%, comparators 0.5%).

Table 6. Drug-related TEAEs in pooled studies

System Organ Class/ Preferred Term	PMF 104 (N=451) n (%)	Comparators (N=439) n (%)
Gastrointestinal Disorders		
Abdominal pain upper	1 (0.2)	1 (0.2)
Dry mouth	1 (0.2)	0
Disgeusia	1 (0.2)	0
Dyspepsia	0	1 (0.2)
Eructation	0	1 (0.2)
Glossodynia	0	2 (0.5)
Oral discomfort	0	1 (0.2)
Vomiting	11 (2.4)	6 (1.4)
General disorders and administration site conditions		
Chills	1 (0.2)	4 (0.9)
Infections and infestations		
Rhinitis	0	1 (0.2)
Investigations		
blood potassium decreased/hypokaliaemia	3 (0.7)	1 (0.2)*
Nervous system disorders		
Headache	23 (5.1)	11 (2.5)
Skin and subcutaneous tissue disorders		
Rash	0	1 (0.2)
Swelling face	0	1 (0.2)
Vascular disorders		
hypertensive crisis/hypertension	1 (0.2)	1 (0.2)

* Two cases were considered not related by the investigators.

PMF 104= Clensia, Comparative treatment concerns SELG 1000 and Moviprep

Serious AEs and deaths

There were no deaths in any of the subjects in the three studies. No subject experienced serious AEs. The incidence of TEAEs resulting in discontinuation was comparable in the Clensia (4 of 451 patients (0.9%)) and comparator (2 of 439 patients (0.5%)) groups.

Laboratory findings

In general, abnormalities in laboratory values occurred at a comparable frequency in patients treated with Clensia and treatment with SELG 1000 or Moviprep. Hypokalaemia has been observed in the clinical studies, at a comparable rate for Clensia and Moviprep. Hyperbilirubinaemia was observed in 3 subjects in the pharmacodynamic study. There was no general trend in hepatic function abnormalities upon Clensia treatment.

Vital signs

Changes in systolic or diastolic blood pressure, pulse rate, body temperature or body weight were observed during the studies. Results of physical examination and vital signs generally gave no reason for clinical concern. There were no clinically meaningful differences observed in mean changes from baseline between treatment groups for vital sign parameters.

Safety in special populations

No subject below 18 years of age was enrolled in the studies. The studies were conducted in Italy, Switzerland and Austria, and the subjects enrolled were predominantly white Caucasians (98.2%) beside a little number of Hispanic subjects (1.6%).

The mean age of subjects enrolled was approximately 55 years (SD ±14.5, median 56, range 18-83). About half of included patients were women. Of the 451 patients in clinical studies receiving Clensia, 123 (27.3%) subjects were aged 65 or older (vs. comparators 31%), while 27 (6%) subjects were over 75 years of age (vs. comparators 7.1%).

Overall, 56 over 631 enrolled subjects aged less than 65 years (8.9%) and 26 over 259 enrolled subjects (10%) aged 65 or older experienced TEAEs. Of the subjects aged more than 65 years, 32.7% experienced at least one TEAE. Occurrence of TEAEs was 24.4% (11 out of 45 patients) for Clensia and 40.5% (15 out of 37 patients) for comparative treatment. In additional analyses, 7.0% (n=10) of patients aged less than 65 years, 10.2% (n=6) of patients aged 65-74 years of age, and 8.3% (n=1) of patients aged 75 years and above experienced TEAEs upon Clensia treatment in study PMF 104 BC1/08. In study PMF BC1/10, proportions of patients experiencing TEAEs upon Clensia treatment in respective age categories were 10.2% (n=15), 11.8% (n=4), and 6.7% (n=1) respectively.

Overall, 12% female vs. 6% male patients had an adverse reaction, and 67% of subjects that experienced at least one TEAE were female. In additional analyses, 7.7% of male patients (n=104) and 8.3% of female patients (n=109) experienced TEAEs upon Clensia treatment in study PMF BC1/08. Respective proportions were 9.7% for male patients (n=93) and 10.7% of female patients (n=103) in study PMF BC1/10.

Clinical safety conclusion
The occurrence of treatment-related TEAEs was overall comparable for Clensia and comparative treatment. None of the included study patients experienced serious AEs.

The use of simeticone
Inert substance simeticone is not absorbed from the gastrointestinal tract and does not interfere with gastric secretion or absorption of nutrient, but is excreted unchanged in the faeces (Park et al., 2009). Because of its mechanism of action and acceptable safety profile, inert active substance simeticone has been included in a variety of medicinal products (e.g. Imodium Duo (UK/H/0241/002)).
Based on the above, it is safe to add simeticone to a Macrogol-electrolyte solution like Clensia.

IV.6 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 Clensia.

Table 7. Summary table of safety concerns as approved in RMP:

Important identified risks	• Fluid and electrolyte abnormalities
Important potential risks	• Potential to temporarily alter absorption of other medicinal products due to a decrease in gastrointestinal transit time • Off-label use in the paediatric population
Missing information	• Paediatric population • Pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

The literature data submitted by the MAH support the use of the active substance combination in Clensia. The pharmacodynamic study showed similarity between Clensia and the reference product SELG 1000. In both clinical efficacy studies, one with SELG 1000 and the other with Moviprep as reference product, test and reference treatment are considered therapeutically equivalent. The addition of simeticone is justified. Comparable bowel cleansing (good to excellent) was observed. Also the safety profile of Clensia is acceptable. Risk management is adequately addressed. This fixed dose medicinal product can be used in adults for bowel cleansing prior to any clinical procedures requiring a clean bowel e.g. bowel endoscopy or radiology.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The 19 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability, including design and lay-out as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Clensia, powder for oral solution has a proven chemical-pharmaceutical quality and is considered an approvable fixed dose combination. All active substances are well known, and are used in combinations in clinical practice.

The pharmacodynamic effects as well as the efficacy and safety profile of Clensia were shown to be comparable to those of other Macrogol-electrolyte solutions indicated for bowel cleansing (SELG 1000 and Moviprep).

The application was discussed in the Board meetings of 14 October 2015 and 23 March 2016. Questions were raised regarding quality aspects and the addition of simeticone to the application. The MAH adequately addressed these quality concerns and provided sufficient data regarding the use of simeticone. Overall, the Board concluded that the benefit-risk balance for this medicinal product is positive.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that Clensia is approvable for the therapeutic indication bowel cleansing, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 June 2016.

VII. REFERENCES

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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