IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Spasmalvex 60 mg/300 mg, soft capsules
ALVERINE CITRATE
Simeticone
PA1927/002/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Spasmalvex 60 mg/300 mg, soft capsules, from Laboratoires Galeniques Vernin on 12th March 2021 for the relief of abdominal pain in irritable bowel syndrome, in adults only.

The HPRA was RMS for this Decentralised Procedure (DCP) and Italy was CMS. This DCP application is a duplicate of the DCP for SimAlvia 60 mg/300 mg, soft capsules which was completed on 10th November 2014 with the UK as RMS. (reference UK/H/5633/01/DC, now IE/H/0600/001/R/001). In the current, duplicate DCP the same applicant, Laboratoires Galeniques Vernin applied for a marketing authorisation for Spasmalvex 60 mg/300 mg, soft capsules.

In line with IE/H/0600/001/DC, the application was submitted under the legal basis of 'well established use' according to Article 10 (a) of Directive 2001/83/EC. No new drug substances are involved in Spasmalvex 60 mg/300 mg, soft capsules. Both active substances in the combination are well-established active substances and have been marketed for more than 10 years, in combination, in the European Union (EU).

Spasmalvex 60 mg/300 mg, soft capsules is subject to prescription which may be renewed.

Name of the product	Spasmalvex 60 mg/300 mg, soft capsules
Name(s) of the active substance(s) (INN)	ALVERINE CITRATE, Simeticone
Pharmacotherapeutic classification (ATC code)	A03AX58
Pharmaceutical form and strength(s)	60/300 mg Capsule soft
Marketing Authorisation Number(s) in Ireland (PA)	PA1927/002/001
Marketing Authorisation Holder	Laboratoires Galeniques Vernin
MRP/DCP No.	IE/H/1028/001/DC
Reference Member State	IE
Concerned Member State	IT

II. QUALITY ASPECTS

II.1 Introduction

This application is for Spasmalvex 60 mg/300 mg, soft capsules

II.2 Drug substance

The active substances are alverine citrate and simeticone, both active substances are described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specifications are considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition Each soft capsule contains 60 mg alverine citrate and 300 mg simeticone.

The excipients in the medicinal product are listed in section 6.1 of the SmPC. A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. / EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

Adventitious Agent Safety
N/A

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects
The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Spasmalvex 60 mg/300 mg, soft capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction
This application for a marketing authorisation was submitted in accordance with Article 10a of Directive 2001/83/EC as amended, a well-established use application. Alverine citrate and simeticone have been in well-established use within the European Union for more than ten years, demonstrating a recognised efficacy and safety profile. A non-clinical overview has been provided, it is based on relevant published literature and written by an appropriately qualified person. In addition a supplementary report and study reports are submitted as supportive data which cover non-clinical toxicology studies conducted with alverine citrate and the proposed combination.

III.2 Pharmacology

The applicant has provided a concise summary of in-vitro and in-vivo studies demonstrating simeticone's efficacy as an anti-flatulent agent. This is related to the anti-foaming activity. Alverine citrate is a non atropinic papaverine-like musculotropic antispasmodic agent with a well characterized pharmacodynamic profile commonly used for the treatment of spasms, abdominal pain or discomfort.

The combination of alverine citrate and simeticone has been assessed in a rat model of distension induced abdominal contractions. The combination was shown to reduce the number of abdominal cramps following three days administration. A summary of secondary pharmacology studies have been submitted and are considered acceptable. No safety pharmacology or drug-drug interaction (DDI) studies for either agent are available, but there is extensive clinical experience with both classes and this is not considered a safety concern.

III.3 Pharmacokinetics

Limited PK data are presented. Simeticone is reportedly physiologically inert, is not absorbed in the GI tract and does not interfere with the absorption of nutrients. Information related to the metabolism of Alverine citrate following human administration has also been summarised. Alverine citrate is reportedly rapidly metabolised to its primary metabolite when administered orally. Peak plasma concentration is reached within 1-1.5 hours following oral dosing with the principal metabolite 7-10 fold more active than alverine. All metabolites are eliminated by active renal excretion. The plasma half-life averages 0.8 hour for alverine and 5.7 hours for the active primary metabolite with parent and metabolites present as glucuro- or sulfo- conjugates in urine.

III.4 Toxicology

Limited data on repeat dose toxicity and carcinogenicity with simeticone in rodents does not suggest a significant cause for concern. Few single-dose and repeat-dose toxicity studies, no reproductive and development toxicity, genotoxicity and carcinogenicity studies have been reported in the literature for alverine citrate or the combination alverine citrate and simeticone.

In order to address the lack of data for alverine citrate, the applicant has provided toxicology study reports performed with alverine citrate and the combination alverine citrate – simeticone (60 mg/300 mg). The overview discusses the data for single and repeat dose toxicity for each component and for the combination. Additional summaries are also provided for genotoxicity, carcinogenicity and for reproductive toxicity.

These supportive studies report that alverine citrate is relatively well tolerated following administration of repeated doses of up to 24 mg/kg orally. At higher doses, effects on blood cholesterol, alanine aminotransferase and liver weight were noted. There were no histopathological correlates of these findings. Toxicity of the combination was assessed following oral administration to rats for periods of 28 days and 13 weeks. No observed effect levels established in these studies were adequately in excess of the proposed clinical dose. Alverine citrate is reported as non-genotoxic in a standard battery of tests. Embryo-foetal development studies conducted in rat and rabbit with the combination did not report a risk of teratogenicity.

III.5 Ecotoxicity/environmental risk assessment

Phase I PEC calculations showed simeticone was above the action limit for phase II assessment. Data related to the phase II assessment did not suggest simeticone is a PBT substance or is likely to pose a risk to the environment. These data were accepted in a previous procedure and were not assessed as part of this procedure.

The applicant has conducted an ERA for alverine citrate as requested in a previous procedure. Phase I PEC calculation showed Alverine is over the action limit and therefore phase II risk assessment was undertaken. LogKow was assessed via the OECD 117 HPLC method and is <4.5, therefore alverine citrate is not considered a PBT substance. The phase II risk assessment consisted of an assessment of physical-chemical properties and fate via OECD 121 and 301F studies. Phase IIa effect studies were carried out in OECD 201, 211, 210 and 209 compliant studies in appropriate species.

The submitted data are in line with what were requested and accepted in a previous procedure. Therefore, no additional queries were raised with regard to the ERA at the time of this procedure and it is accepted that alverine citrate does not pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

Alverine citrate and simeticone have been in well-established use within the European Union for more than 10 years, demonstrating a recognised efficacy and safety profile. An abridged dossier was submitted in accordance with Article 10a of Council Directive 2001/83/EEC as amended. The non-clinical evidence in support of this application is based on relevant

published scientific literature as well as submitted study reports which is appropriate and the findings are appropriately summarised in the submitted SmPC.

Substance (INN/Invented Name): Alverine citrate					
CAS-number (if available):5560-59-8					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 117	3.93 ± 0.003 at pH 7			Potential PBT (N)
PBT-assessment					
PBT-statement :	The Alverine is not considered bioaccumulative or toxic based on the data available.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.9	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	Koc< 10000 L/Kg			Terrestrial assessment, not triggered.
Ready Biodegradability Test	OECD 301F	Not readily biodegradable			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Ratio PEC/PNEC**		**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	72 hr NOEC	surface water= 0.52		Pseudokirchneriella subcapitata
Daphnia sp. Reproduction Test	OECD 211	NOEC		Groundwater=0.13	Reproduction
Fish, Early Life Stage Toxicity Test/*Danio Rerio*	OECD 210	30 day NOEC			Survival
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	Microorganism=0.002		

Neither Alverine citrate nor simeticone are a PBT substance. Considering the above data, alverine citrate and simeticone is not expected to pose a risk to the environment.

III.1 Discussion on the non-clinical aspects

Alverine citrate and simeticone have been in well-established use within the European Union for more than 10 years, demonstrating a recognised efficacy and safety profile. An abridged dossier was submitted in accordance with Article 10a of Council Directive 2001/83/EEC as amended. The non-clinical evidence in support of this application is based on relevant published scientific literature as well as submitted study reports which is appropriate and the findings are appropriately summarised in the submitted SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Spasmalvex 60 mg/300 mg, soft capsules contains the combination of two active substances, alverine citrate 60 mg and simeticone 300 mg which have been authorised in combination in the EU (FR) since 1991. Alverine citrate is a non-atropinic, papaverine-like anti-spasmodic agent which relieves gastro-intestinal smooth muscle spasm. Simeticone is a physiologically inert, hydrophobic substance which gives symptomatic relief of gas-related abdominal discomfort such as bloating, cramping or flatulence.

Irritable Bowel Syndrome (IBS) is a complex, gastro-intestinal, functional bowel disorder (FBD) identified by symptoms attributable to the middle or lower gastrointestinal tract, particularly abdominal pain, once other diagnoses are excluded.

This application was submitted under the legal basis of 'well established use' according to Article 10 (a) of Directive 2001/83/EC. No new drug substances are involved in Spasmalvex 60 mg/300 mg, soft capsules. Both active substances in the combination are well-established active substances and have been marketed for more than 10 years, in combination, in the European Union (EU).

The applicant has submitted bibliographic evidence to demonstrate the safety and efficacy of the combination of active substances, which is appropriate for this type of application. No new clinical studies are needed for this duplicate application. The dossier also contains evidence of bioequivalence with the well-known alverine citrate – simeticone (60 mg/300 mg) European marketed product authorised since 1991 and references non-clinical, clinical and post-marketing data related to this product to demonstrate safety and efficacy.

The content of the SmPC approved during this DCP is in accordance with the currently approved SmPC for SimAlvia 60mg/300mg, soft capsules.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

The pharmacokinetics (PK) of each active substance individually and in combination are well-known. The applicant provided a review and discussion of published PK data considered adequate to support the proposed use of Spasmalvex 60 mg/300 mg, soft capsules. A brief summary follows.

Alverine is absorbed from the gastrointestinal tract after oral doses and is rapidly metabolized to the active metabolite para-hydroxy alverine, peak plasma concentrations of which occur 1 to 1.5 hours after an oral dose. Further metabolism to inactive metabolites occurs, and these are excreted in the urine by active renal secretion. With a $T_{1/2}$ of 12.5 hours, steady-state for plasma concentrations of alverine are reached within 5 days. A clinical study confirmed that alverine crosses the gastro-intestinal barrier with inter-individual variability. However in most patients, plasma concentrations were lower than 1ng/ml.

Simeticone is not absorbed from the gastrointestinal tract. Following oral administration, it is eliminated in unchanged form in the faeces. As simeticone is physiologically inert, does not interfere with gastric secretion and does not interfere with the absorption of nutrients its combination with alverine citrate is not expected to change the PK pattern of alverine or its active metabolite para-hydroxy alverine.

No relevant interactions between the combination product SpasmAlvex 60 mg/300 mg, soft capsules and other drugs are anticipated.

IV.3 Pharmacodynamics

Alverine citrate is a non-atropinic, papaverine-like musculotropic antispasmodic which, in recommended doses, reduces the tone of smooth muscle of the gastrointestinal tract. The suggested mechanism of action includes blocking of calcium channels located in the smooth muscle.

Simeticone is a physiologically inert and pharmacologically inactive substance. Simeticone acts by modifying the surface tension of gas bubbles, thus causing their coalescence and making elimination easier and quicker, which contributes to IBS symptom control.

No relevant interactions between the combination product SpasmAlvex 60 mg/300 mg, soft capsules and other drugs are anticipated.

IV.4 Clinical Efficacy

No new dose response studies were submitted with this application, which is acceptable for a duplicate DCP on the legal basis of article 10a, well-established use. The efficacy of SpasmAlvex (alverine citrate – simeticone) 60 mg/300 mg, soft capsules in Irritable Bowel Syndrome (IBS) is based on evidence of symptomatic relief of smooth muscle spasm and relief of bloating, leading to the overall relief of abdominal pain. The applicant has adequately summarised the clinical trial data indicating efficacy of the combination product versus placebo, versus active comparators. The dossier also contains a bioequivalence study which demonstrated that the applicant's alverine citrate – simeticone 60 mg/300 mg, soft capsule combination is similar to the alverine citrate – simeticone (60 mg/300 mg) European marketed product.

IV.5 Clinical Safety

The applicant has adequately summarised the clinical data supporting the safety profile of SpasmAlvex (alverine citrate – simeticone) 60 mg/300 mg, soft capsules in IBS, citing evidence from double blind trials, observational clinical data from usual clinical practice, ICSRs retrieved from the literature and post-marketing pharmacovigilance data.

The safety data of alverine citrate – simeticone (60 mg/300 mg) European marketed product supports the safety of Spasmalvex 60 mg/300 mg, soft capsules: Like all medicines this medicine can cause side effects although not everybody will experience these. For information about potential side effects which may occur when taking Spasmalvex 60 mg/300 mg, soft capsules please refer to the SmPC or package leaflet. No new significant concerns that required risk management or risk minimization processes other than routine pharmacovigilance measures and product labelling were identified.

IV.6 Risk Management Plan (RMP)

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 Spasmalvex. The submitted Risk Management Plan, version 5.1, signed 29th April 2020 is considered acceptable. Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed. Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed. The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary table of safety concerns as approved in the RMP:

Summary of Safety Concerns	
Important Identified Risks	- **Hepatobiliary Disorders**: Hepatitis, hepatocellular injury, Liver enzymes increased
	- **Immune system disorders:** Hypersensitivity, anaphylactic reaction including shock, oedema, urticaria
Important Potential Risks	None
Important missing information	None

IV.7 Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.8 Discussion on the clinical aspects

This duplicate DCP application is for marketing authorisation for Spasmalvex 60 mg/300 mg, soft capsules indicated for relief of abdominal pain in irritable bowel syndrome, in adults only, with the original DCP for SimAlvia 60 mg/300 mg, soft capsules having concluded positively in 2014.

The clinical pharmacology, efficacy and safety of both active substances in combination are well known and adequately discussed in the submitted dossier.

In conclusion, the evidence from listed studies, published literature and post marketing data, taken together, is considered sufficient to support the efficacy and safety of Spasmalvex 60 mg/300 mg, soft capsules for the relief of abdominal pain in irritable bowel syndrome, in adults only.

V. OVERALL CONCLUSIONS

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

The HPRA, on the basis of the data submitted, considered that Spasmalvex 60 mg/300 mg, soft capsules has demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

18.11.2025

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE