Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

SimAlvia 60 mg/300 mg, soft capsules

(alverine citrate and simeticone)

Procedure No: UK/H/5633/001/DC

UK Licence No: PL 15490/0001

Laboratoires GALENIQUES VERNIN

LAY SUMMARY
SimAlvia 60 mg/300 mg, soft capsules
(alverine citrate and simeticone)

This is a summary of the public assessment report (PAR) for SimAlvia 60 mg/300 mg, soft capsules (PL 15490/0001). It explains how SimAlvia 60 mg/300 mg, soft capsules were assessed and their authorisation recommended as well as the conditions of use. It is not intended to provide practical advice on how to use this product. This medicinal product will be referred to as SimAlvia soft capsules in the remainder of this report.

For practical information about using SimAlvia soft capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are SimAlvia soft capsules and what are they used for?
SimAlvia soft capsules are a medicine with a 'well-established use'. This means that the medicinal use of the active substances of SimAlvia soft capsules have been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

SimAlvia soft capsules reduce the muscle contractions of the gut and flatulence (gas). It is used to relieve pain associated with contractions (spasms) of the intestine and bloating.

How are SimAlvia soft capsules used?
SimAlvia soft capsules are taken by mouth. A whole capsule should be swallowed with a glass of water at the beginning of meals.

This medicine is for adults only and the recommended dose is 1 capsule 2 or 3 times a day.

SimAlvia soft capsules can only be obtained on prescription from a doctor.

For further information on how SimAlvia soft capsules are used, refer to the Summary of Product Characteristics or package leaflet available on the MHRA website.

How do SimAlvia soft capsules work?
SimAlvia soft capsules contain two active ingredients, alverine and simeticone. Alverine belongs to a class of drugs called musculotropic antispasmodics, which relieves crampy pain in the lower tummy (abdomen). Simeticone belongs to a class of medicines called antiflatulents and relieves bloating and reduces gas related discomfort.

What benefits of SimAlvia soft capsules have been shown in studies?
As alverine and simeticone are well-known substances, and their use to relieve pain associated with contractions (spasms) of the intestine and bloating is well-established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of alverine and simeticone in the treatment of pain associated with contractions (spasms) of the intestine and bloating.

In addition, the company (Laboratoires GALENIQUES VERNIN) has provided a discussion of the bioequivalence study conducted with the originator combination as well as study reports for the combination and a single active alverine to support the efficacy and safety of this product.

What are the possible side effects of SimAlvia soft capsules?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For information about side effects that may occur when using SimAlvia soft capsules, please refer to the

package leaflet or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Why are SimAlvia soft capsules approved?
It was considered that the benefits of SimAlvia soft capsules outweigh the risks, and the grant of this Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of SimAlvia soft capsules?
A risk management plan has been developed to ensure that SimAlvia soft capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for SimAlvia soft capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about SimAlvia soft capsules
Belgium, Republic of Ireland and the UK agreed to grant a Marketing Authorisation for SimAlvia soft capsules on 10th November 2014. A Marketing Authorisation was granted in the UK on 8th December 2014.

The full PAR for SimAlvia soft capsules follows this summary. For more information about treatment with SimAlvia soft capsules, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in August 2016.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for SimAlvia 60 mg/300 mg, soft capsules (PL 15490/0001) for the relief of abdominal pain in irritable bowel syndrome, is approvable. This product will be referred to as SimAlvia soft capsules throughout this report.

SimAlvia soft capsules are indicated in adults only.

This application was submitted according to Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use. Therefore the evidence provided to demonstrate the safety and efficacy of this product is bibliographic in nature, which is appropriate for applications of this type.

The medicinal product contains the active ingredients alverine citrate, a non-atropinic, papaverine-like musculotropic antispasmodic, and simeticone, an inert substance which has a physical action by altering the surface tension of gas bubbles, leading to their coalescence.

With the UK as the RMS in this Decentralised Procedure (UK/H/5633/001/DC), Laboratoires GALENIQUES VERNIN applied for the Marketing Authorisation for SimAlvia soft capsules in Belgium and the Republic of Ireland.

Bibliographic data on alverine and simeticone have been submitted to support this application. In addition to the submission of published non-clinical and clinical references, the applicant has also included a discussion of the bioequivalence study conducted with the originator combination and has also provided study reports for the combination and a single active alverine citrate formulation.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 10th November 2014). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 15490/0001) for this product on 08 December 2014.

II QUALITY ASPECTS

II.1 Introduction

SimAlvia soft capsules contain 60 mg alverine citrate and 300 mg simeticone, as active ingredients. The excipients present in this product are gelatin, glycerol, titanium dioxide (E171) making up the soft capsule shell and the external lubricant is composed of soya lecithin and fractionated coconut oil.

All excipients used comply with their respective European Pharmacopoeia or United States Pharmacopeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

The only excipient used that contains material of animal or human origin is gelatin. Satisfactory documentation has been provided by the gelatin suppliers stating that the gelatin they provide complies with the criteria described in the current version of the monograph 'Products with risk of transmitting agents of animal spongiform encephalopathies'. Confirmation has also been given that the glycerol used in the capsules is of vegetable origin.

The finished product is packaged in polyvinylchloride (PVC)/aluminium thermoformed blisters of 10 soft capsules. The pack sizes are 10, 20, 30, 40, 60 or 90 capsules. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

Simeticone

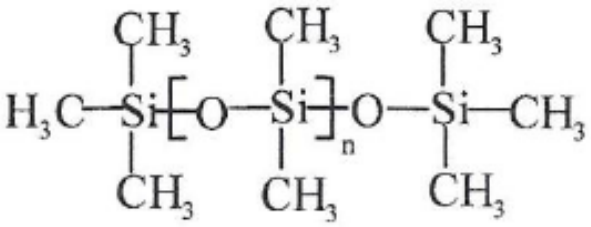
INN: Simeticone

Chemical name(s): Mixture of polydimethylsiloxane (PDMS) fluid and silica.

1. Polydimethylsiloxane (PDMS) (α-ώ-bis-trimethylsiloxypolydimethylsiloxane)
2. Fumed silica: SiO_2

Structure:

PDMS



Fumed Silica: SiO_2

Molecular formula: $(CH_3)_3Si\text{-}(O\text{-}Si(CH_3)_2)_n\text{-}O\text{-}Si(CH_3)_3$, SiO_2
Molecular weight: Not applicable
Appearance: Translucent grey liquid.

Simeticone is the subject of a European Pharmacopoeia monograph.

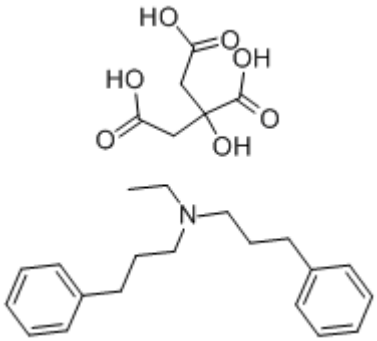
All aspects of the manufacture and control of the active substance, simeticone, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Alverine citrate

INN: Alverine citrate

Chemical name(s): *N*-ethyl-3-phenyl-*N*-(3-phenylpropyl)propan-1-amine dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate
N-ethyl-*N*-(3-phenylpropyl)-benzenepropanamine, citrate

Structure:



Molecular formula: $C_{26}H_{35}NO_7$
Molecular weight: 473.56 g/mol
Appearance: A white to pale yellow fine powder.
Solubility: Slightly soluble in water and in methylene chloride, sparingly soluble in ethanol.

Alverine citrate is the subject of an active substance master file (ASMF).

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specification. Certificates of Analysis for all working standards have been provided.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the pharmaceutical development programme was to obtain a safe, efficacious, stable soft capsule containing 60 mg alverine citrate and 300 mg simeticone.

Suitable pharmaceutical development data have been provided for this application.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using the minimum commercial scale batch sizes and has shown satisfactory results. The applicant has committed to perform validation on the first three full scale commercial batches.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability of the products
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 30 months with storage conditions "Store below 25°C" and "Keep in outer carton in order to protect from light" have been set. These are satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of alverine citrate and simeticone are well-known. Bibliographic data on alverine and simeticone have been submitted to support this application. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A review of the toxicity data is provided. This encompasses literature for simeticone, supportive study data for alverine citrate and combination studies using alverine citrate – simeticone. Although the use of the study data to support a well-established use application is not ideal it is acknowledged that the gap in knowledge are substantial for toxicology sections and the applicant's robust justification for using the supportive data can be accepted.

III.2 Pharmacology
Alverine citrate is a non atropinic papaverine-like musculotropic antispasmodic agent, commonly used in the treatment of spasms, abdominal pain or discomfort related to functional bowel disorders. Simeticone is a hydrophobic substance with anti-foaming effect.

The applicant's conclusion that the spasmolytic properties of alverine and the anti-flatulent and protective properties of simeticone on gastric mucosa are widely recognised and have been well demonstrated both *in vitro* and *in vivo* in animal models is acknowledged, the combination of alverine citrate and simeticone appears to be a new combination in the UK.

III.3 Pharmacokinetics
Following oral administration, alverine citrate is absorbed from the gastrointestinal tract and is rapidly metabolised to an active metabolite and inactive metabolites. Metabolites are excreted in the urine by active renal excretion.

Simeticone is not absorbed from the gastrointestinal tract. Following oral administration, it is eliminated in unchanged form in the faeces.

The pharmacokinetics of alverine citrate and simeticone have not been discussed in detail in the non-clinical overview. Due to the lack of pharmacokinetic animal data, the pharmacokinetic properties of alverine citrate in the combination alverine citrate and simeticone have been investigated in humans.

III.4 Toxicology

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 and simeticone. 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. A review of the toxicity data is provided which covers literature for simeticone, supportive study data for alverine citrate and combination studies using alverine citrate – simeticone.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The applicant has committed to provide a complete environmental risk assessment (ERA) for alverine citrate once relevant studies are complete. No environmental risk from the use of simeticone is anticipated.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this product from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction

Alverine citrate and simeticone are well-known substances and the details of their pharmacokinetics are documented in various publicly accessible sources that the applicant has adequately summarised in the clinical overview. Bibliographic data on alverine and simeticone have been submitted to support this application. In addition, the applicant has also included a discussion of the bioequivalence study conducted with the originator combination and has also provided study reports for the combination and a single active alverine citrate formulation.

IV.2 Pharmacokinetics

The applicant has included discussion of the bioequivalence study conducted with the originator combination and has also provided study reports for the combination and a single active alverine citrate formulation.

The F-test and T-test comparison of the 2 primary parameters C_{max} and AUC of the applicant's product versus Spasmonal used for the pharmacokinetic (PK) profile comparison according to the guideline CPMP/EWP/QWP/1401/98, show that:

- Their values are comparable, the calculated F, respectively 1.31 for C_{max} and 1.14 for AUC_t, are below the tabulated F0.05, 78, 79= 1.45;

- Their means are not statistically different; the probabilities being respectively of 0.84 for the C_{max} and 0.60 for AUC_t (T test $p>0.05$)

Moreover the comparison of the C_{max} and AUC_t of the two reference products Spasmonal® (alverine citrate 60 mg) and Meteospasmyl® (alverine citrate 60 mg - simeticone 300 mg) leads to similar results and confirms the validity of the above comparison. There is no statistical difference between C_{max} and AUC_t related to alverine citrate alone or combined with simeticone as well as for the F-test and for the T-test.

After oral administration, alverine is known to be mainly metabolised in the liver and rapidly converted to its primary active metabolite, which is then further converted to secondary metabolites. There is a high renal clearance of all metabolites indicating that they are eliminated by active renal secretion. The peak plasma level of the most active metabolite occurs between 1 and 1½ hours after oral dosing. The plasma half-life averages 0.8 hours for alverine and 5.7 hours for the active primary metabolite. Simeticone is not systemically absorbed.

IV.3 Pharmacodynamics

Alverine is a spasmolytic agent with a direct effect on the smooth muscle of the gastrointestinal tract (the effect of alverine is similar to the effect of papaverine). Suggested mechanism of action includes blocking of calcium channels located in the smooth muscle. Alverine is more effective and less toxic than papaverine. In recommended doses, alverine reduces the tone of smooth muscle of the gastrointestinal tract. Simeticone is a physiologically inert substance, which is therefore pharmacologically inactive. Due to its physical properties, simeticone decreases the formation of gas and facilitates its removal from the digestive tract. It acts by modifying the surface tension of gas bubbles, thus causing their coalescence and making their elimination easier and quicker. Orally administered simeticone forms a protective liner on the intestinal mucosa.

In a study, thirty eight patients diagnosed with Irritable Bowel Syndrome (IBS) were investigated and their visceral sensitivity assessed with the rectal balloon distension test using an electronic barostat, at baseline and after a course of alverine citrate - simeticone 60 mg/300 mg (ACS) during 2 weeks. The results have shown a significant reduction of the pain threshold after alverine citrate - simeticone 60 mg/300 mg therapy. An increase of the pain sensitivity threshold has been observed in 95% of the IBS patients and 22% of them have normalised their respective value after ACS course.

IV.4 Clinical efficacy

A multicentre, double blind, placebo controlled, randomised study conducted in Hungary and Poland was primarily designed to investigate whether patients suffering from IBS had a greater relief of their abdominal pain/discomfort, when treated with ACS combination for 4 weeks compared to placebo. The primary objective was to assess the efficacy and safety of ACS combination, 3 capsules per day for 4 weeks, compared to placebo. Four hundred and twelve (412) patients with IBS defined by Rome III criteria were enrolled (ACS arm: 207; placebo arm: 205). At baseline, abdominal pain/discomfort severity was comparable between the groups with a visual analogue scale (VAS) mean score of 72.2±7.5 mm and 74.2±8.5 mm in the ACS and placebo groups respectively. Other patient characteristics were also comparable in both groups at baseline. Only 3.0% of patients failed to complete the study, and overall compliance was excellent, estimated at greater than 96% in both groups. The analysis of the primary efficacy criterion used a non-parametric rank-based analysis of covariance (Quade's analysis) and highlighted a statistically significant difference (p=0.0467) between the 2 groups in favour of ACS. The median VAS score at week 4 was 40.0 mm for the ACS group compared with 50.0 mm for the placebo group. This result was supported by the qualitative analysis based on responders at week 4 with an additional 12.5% of responders in the ACS group (46.8%) compared with placebo (34.3%). The difference was statistically significant (OR= 1.30; p=0.010).

In two prospective randomised double-blind trials, carried out in the early 1990s in France, ACS was compared to other antispasmodics broadly prescribed in Europe for the treatment of functional bowel diseases (FBD) and for IBS: trimebutine and mebeverine. All preparations were administered at the approved dosages. The principal assessment criterion was abdominal pain using the Cook score (1991), containing 3 items: intensity, duration, and frequency with a 7-point scale (0 = absence and 6 = maximum), with addition of the 3 scores to obtain a total. The overall pain score could thus range from 0 to 18. Overall, 239 patients were randomised, 122 in the ACS groups and 117 in the comparative groups. No statistically significant difference was found between ACS and mebeverine on pain relief when administered for 42 days. However, a statistically significant increase in efficacy of ACS over trimebutine was shown on D56 on both the total pain score and pain intensity. Intragroup analysis comparison over the time versus Day 0 of the abdominal pain (principal criterion) indicates a statistically significant reduction of Cook’s score at Day 21 and Day 42 for both groups of treatment. However the intergroup analysis of the main criteria did not demonstrate any statistical difference between the two groups. It demonstrated the effectiveness of both treatments for the treatment of IBS, with no difference between the two treatment groups which was the initial hypothesis. Therefore the non-inferiority of alverine citrate - simeticone 60 mg/300 mg soft capsule is demonstrated when

considering the literature data on IBS, the choice of active comparators, groups' comparability at Day 0 and the primary endpoints assessed in these two controlled clinical trials.

A study compared the effectiveness of two treatment strategies in IBS adult patients in France: on demand treatment with ACS versus usual treatment, over 6 months. This randomised, controlled pragmatic study was performed on two parallel groups of IBS patients. Eighty seven general practitioners were randomly allocated to one of the two treatment strategy arms. The primary endpoint was the magnitude of change in the total score of the health-related quality of life between treatment groups, assessed by a disease specific scale (IBSQoL) from baseline to month 6. In total, 436 patients were enrolled (ACS group: 222; Usual treatment: 214). Baseline patient characteristics were similar in the two study groups. At inclusion, 93.8% of patients reported moderate to severe abdominal pain. The adjusted mean (SE) change of the IBSQoL total score, from baseline to month 6, was significantly higher in the on-demand ACS group compared with the usual treatment group: 13.8 (1.1) versus 8.4 (1.2) with a difference between groups of 5.4 (95% CI: 2.3-8.6; p=0.0008). All other end points favoured ACS over the normal therapy. The results of this pragmatic study are consistent with those obtained in the placebo-controlled study and highlight the interest and relevance of an on-demand treatment approach with ACS in patients with any subtype of IBS.

A prospective, multicenter, non-interventional study at 26 Chinese sites (from December 2010 to January 2012) enrolled 640 subjects diagnosed with IBS according to ROME III criteria (52.3% male: mean age: 43.6 ± 12.5 years). They all presented with abdominal pain and discomfort ≥60 of 0 - 100 VAS. Patients received alverine citrate (60 mg) with simeticone (300 mg) (ACS) 3 times daily for 4 weeks. Pain/discomfort and bloating/distension were assessed by VAS. Global symptoms and QOL were assessed by 7-point and 5-point Likert scales, respectively. Post-treatment bowel function was assessed by Bristol Stool Form Scale (BSFS) and treatment-related adverse events (AEs) were recorded. Of 640 patients, 540 (84.4%) completed the study, and 100 (15.6%) withdrew. In total, 87.5% reported bloating at baseline. After 4-week ACS treatment, 89.1% reported global symptom improvement. Furthermore, 4-week ACS treatment reduced pain and bloated VAS scores significantly from 78.4 ± 9.9 to 32.1 ± 21.0 and from 63.2 ± 27.2 to 22.6 ± 20.9, respectively (both $p < 0.001$), decreased diarrhoea or constipation occurrence from 67.2% to 10.2% ($p < 0.001$), and reduced IBS impact on QOL with only 2 treatment-related AEs. The authors concluded that routine clinical administration of alverine citrate and simeticone combination for IBS over a 4-week period provides effective relief of IBS symptoms and improves QOL in IBS patients.

An open study was conducted in Russia with 53 patients who were diagnosed with IBS in accordance with Rome III criteria (mean age: 36.2 ± 12.8 years). 21 patients were diagnosed with IBS with predominance of pain and bloating (IBS-A), 17 with constipation (IBS-C), 15 with diarrhoea (IBS-D). They received ACS as a monotherapy over 2 weeks. All patients were tested for pain prior to and after the treatment with a balloon dilatation test. After treatment the pain completely resolved in 90.5% of patients with IBS-A, in 64% of patients with IBS-C, and 72% of patients with IBS-D. Bloating resolved in 100% of patients with IBS-C, in 86% of patients with IBS-A, and in 53% of patients with IBS-D. More than half (56%) of the patients with IBS-D had normalised stool after treatment. On IBS-C patients the treatment was not as effective with only 27% of them having normalised stool after treatment. The lowest values of the threshold for pain sensitivity were observed in patients with IBS-D. The most pronounced effect on pain was observed in patients with IBS-A with a normalised pain threshold for 55% of them. Authors are concluding that alverine citrate and simeticone combination treatment is a treatment of choice for IBS-A patients.

A controlled multicentric, double blind, cross over study in 27 IBS patients over 2 weeks for each period was conducted. The primary objective was to evaluate the effects of alverine citrate versus placebo on rectal sensitivity in patients with IBS. They have demonstrated that patients in the alverine citrate group had a significant improvement between D0 and D14 in the distension index ($p<0.01$) and in the volume required to induce the maximal bearable sensation ($p<0.05$) when performing rectal distension. This

difference has been mainly explained by a significant reduction of sensitivity in the alverine citrate group whereas no evolution was observed in the placebo group, confirming alverine citrate activity on the digestive sensitivity.

A randomised, double-blind, cross-over study in 45 IBS patients comparing alverine citrate versus mebeverine hydrochloride was conducted. After a two-week placebo run-in period, patients were treated for four weeks with one of these drugs, followed by four weeks on the other, in random order. The results confirmed that both alverine citrate and mebeverine hydrochloride are beneficial in treating the symptoms of IBS.

The applicant has also bridged to the originator product from France with a bioequivalence study looking at alverine citrate as it is systemically absorbed. The results are discussed below:

This four-period, two-sequence, cross-over, controlled, block randomised, single dose, replicate design bioequivalence study has been conducted from 20th May 2011 to 29th June 2011. The aim of this study was to compare the extent and rate of absorption of the proposed formulation of Alverine - simeticone soft capsules 60 mg/300 mg, following a 60 mg/300 mg single oral dose (1 soft capsule of test formulation) versus an equal dose of reference formulation (one soft capsule of Meteospasmyl® 60 mg/300 mg – Mayoly Spindler, France), each given twice (on two different occasions according to a 4 period cross over replicate design), to healthy volunteers, in fed conditions. The fed condition was chosen based on the reference product SmPC which recommends taking the product at the beginning of meals. Considering that alverine citrate is a highly variable drug a replicate design has been deemed more suitable than a standard two-way cross over design. The bioanalytical method of this study performed by a liquid chromatography/mass spectrometry (HPLC/MS) method is consistent with the guideline on bioanalytical method validation (EMA/CHMP/EWP/192217/2009) and with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**).

The 90% confidence intervals of geometric mean ratios were fully within the accepted 80.00-125.00% bioequivalence range, leading to the conclusion of bioequivalence with respect to AUC_{0-t} and C_{max}. No further widening interval criteria were further applied on C_{max} as the bioequivalence was proven on the normal 80.00-125.00% regulatory range.

This study has shown bioequivalence for the alverine citrate element of the combination with the French originator product. This allows for bridging to the data above using the combination.

The applicant also compared the availability of alverine citrate in combination and on its own, in two studies:

The aim of the first study (ALSI-PKP-04-IPC/13) was to assess the pharmacokinetic profile of alverine citrate following a single oral dose of the European reference product Meteospasmyl® soft capsules (alverine citrate – simeticone 60 mg/300 mg), to healthy volunteers, under fed conditions. The pharmacokinetic profile assessment was based on plasma drug levels of alverine and its metabolites 4-hydroxy-alverine and N-desethylalverine. Apart from the complete PK data generated to characterise the pharmacokinetic profile of alverine citrate from the reference product, this study confirmed a very high intersubject variability of the main PK parameters (C_{max}, AUCs) and that the metabolisation of alverine citrate is extensive. The second study (ALC-BESD-02-IPC/11) characterised the pharmacokinetic profile of alverine citrate following a single oral dose of the European reference product Spasmonal® (alverine citrate 60 mg, hard capsule) and also confirming a very high intersubject variability. Comparing the pharmacokinetic data from these two studies with the applicant's product PK data obtained from the bioequivalence study ALSI-BEFI-03-IPC/10 leads to the conclusion that:
- Simeticone (300 mg) administered in combination with alverine citrate (60 mg) does not modify alverine citrate pharmacokinetic parameters;
- The pharmacokinetic profile of alverine citrate is similar between the applicant's product and the

European reference product containing alverine citrate 60 mg alone (Spasmonal®).

No formal comparison is presented.

The applicant has also compared the *in vitro* defoaming activity of simeticone in the applicant's formulation and that of the originator product. A bioequivalence study is not possible as simeticone is not systemically absorbed. It complies with the Ph. Eur. simeticone monograph. The results show that the defoaming activity is similar.

The applicant has also shown well-established use for the combination using the sales figures from the French originator product, showing that sales since launch in 1991 support its use.

Conclusions:
Overall, the body of data provided by the applicant supports the position that the use of the combination is well-established. The bioequivalence study looking at alverine citrate in the originator and proposed combination shows equivalence, bridging to the data provided (sales and bibliographic efficacy) of the product licenced in France. For simeticone, the comparison of defoaming properties showed similarity. The data presented also shows that alverine citrate, as a separate active is more effective than placebo in the indications proposed and it is as effective as mebeverine which is also used in similar indications. From this, efficacy of the separate actives and the combination can be concluded.

IV.5 Clinical safety

The study versus placebo included 412 patients, 207 in the ACS group and 205 in the placebo arm.
In this study, the incidence of adverse events was similar in both groups with 17.9% and 24.4% of patients reporting at least one treatment emergent adverse event (TEAE) under ACS and placebo respectively. TEAEs reported by at least 2% of patients are provided. Seven (3.4%) patients in the ACS group and 12 (5.9%) in the placebo group reported TEAEs defined as possibly related to study drug by the investigators. There were no deaths or other drug-related serious adverse events in that study. Only one patient in the ACS group experienced a traumatic tendon rupture which was not considered drug-related. Three patients, one in the ACS group and two in the placebo group, withdrew from the study due to TEAEs, eye swelling in the ACS patient and dizziness and pain in the extremities in the placebo patients.

The other randomised double blind, comparative studies, conducted between 1991 and 1996 included 239 patients, 122 patients in the ACS groups and 117 patients in the comparators' groups.
Adverse event incidence was 5.1% in patients exposed to ACS and 11% in the comparators' group. All adverse events were benign. No severe adverse events and no unexpected adverse events were reported. Treatment discontinuations due to adverse events were rare (1%) and no age-related specificity was observed.

The safety population of this pragmatic study comparing on demand ACS treatment versus usual treatment, included 432 patients (ACS: 222; Usual treatment: 210). All adverse events were recorded. At least one adverse event was reported by 90 patients (40.5%) in the on-demand ACS group and 86 patients (41.0%) in the usual treatment group. No serious adverse event was drug-related. A total of 2.2% of patients experienced adverse effects considered by the investigators as possibly related to ACS treatment, while no adverse event was designated as IBS drug-related in the usual treatment group.

In an open, multicentre, prospective study of ACS efficacy and safety in patients with IBS (Rome II criteria), run between February and August 2005 in Mexico, the objective was to evaluate the efficacy and safety of ACS over a 4-week treatment period, in routine clinical practice.
Safety assessment was based on the occurrence of any adverse event, including concomitant disease resulting in deterioration of a patient's well-being independent of a causal relationship with the study drug. The safety population included 914 IBS patients. Overall 85 patients (9.3%) experienced 113

adverse events. The adverse events were considered as mild in 73 patients (85.9%), moderate in 12 patients (14.1%) and severe in 7 patients (0.8%). Most adverse events were mild to moderate digestive symptoms that did not require treatment discontinuation, except in 4 patients (1 for flatulence, 1 for distension, 1 for pain, distension and constipation, 1 for distension and flatulence). These events abated spontaneously and were not considered treatment-related.

Five cases of alverine citrate induced hepatitis were published as individual safety reports in the international literature.

"Hepatobiliary disorders" have been reported with Meteospasmyl® in post-marketing experience and include jaundice, reversible transaminases increased and hepatitis.
From January 2000 to December 2013, a total of 47 cases of liver disorders (including the 5 published cases) were reported to Laboratoires Mayoly Spindler:
- 6 case reports were considered as unlikely to be related to Meteospasmyl® intake due to either a pre-existing liver disease or a biliary lithiasis discovered by complementary examinations;
- 22 case reports with a causal relationship were considered as doubtful;
- 16 case reports with a causal relationship were considered as possible;
- 3 case reports with a causal relationship were considered as probable;

Hepatobiliary disorders had a favourable outcome in all cases, except in one case reporting a fulminant hepatitis requiring liver transplant in a depressive woman. In that case, due to concomitant treatments (iproniazide for 3 to 6 months and self-administration of paracetamol up to 6g/day for 15 days) and due to the events chronology (Meteospasmyl® given after the first liver injury symptoms occurrence, diagnosis confirmed only 4 days after Meteospasmyl® initiation and drugs discontinuation only 12 days after the diagnosis), the causal relationship with Meteospasmyl® was considered as doubtful.
Hepatobiliary disorders incidence remains very low (19 cases are possibly or probably related to Meteospasmyl® over the period from 2000 to 2013) in spite of the extensive use of the product. In most cases there is no uniquivocal diagnosis and the pre-clinical data analysis failed to show any evidence of hepatotoxicity potential. Hepatobiliary disorders are already listed in the SmPC. No risk factor has been identified.

Conclusion:
The data provided demonstrates the well-established safety of the combination. The trial data shows low rates of mild adverse events, demonstrating a relatively benign adverse event profile. The post marketing experience is reassuring given the large sales volume and relatively few events.

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 ALVERINE-SIMETICONE soft capsules.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hepatobiliary Disorders: Liver enzymes increased, Hepatitis, Hepatocellular injury	***Information included in Alverine - Simeticone 60mg/300mg soft capsule SmPC*** **4.1 Therapeutic indications** **4.2 Posology and method of administration** **4.3 Contraindications** **4.8 Undesirable effects**	NO
Immune system disorders : Hypersensitivity, Anaphylactic reaction, Urticaria, Laryngeal œdema, Shock		NO
Use outside the labelled dose, duration or indication	***Information included in the package leaflet for Alverine - Simeticone 60mg/300mg soft capsule*** **1. WHAT ACS CAPSULES ARE AND WHAT THEY ARE USED FOR** **2. BEFORE YOU TAKE ACS CAPSULES** **3. HOW TO TAKE ACS CAPSULES** **4. POSSIBLE SIDE EFFECTS**	NO

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended.

V USER CONSULTATION

The package leaflet has been evaluated for SimAlvia soft capsules via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use.*

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. This application includes an adequate review of published non-clinical and clinical data concerning the safety and efficacy of alverine citrate and simeticone. Alverine citrate and simeticone are well-known active substances with established efficacy and tolerability. The clinical dossier, using a number of methods, including bibliographic data, in-use data and comparisons to approved products has been shown to be safe and efficacious in the requested indications. The benefit/risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Labelling

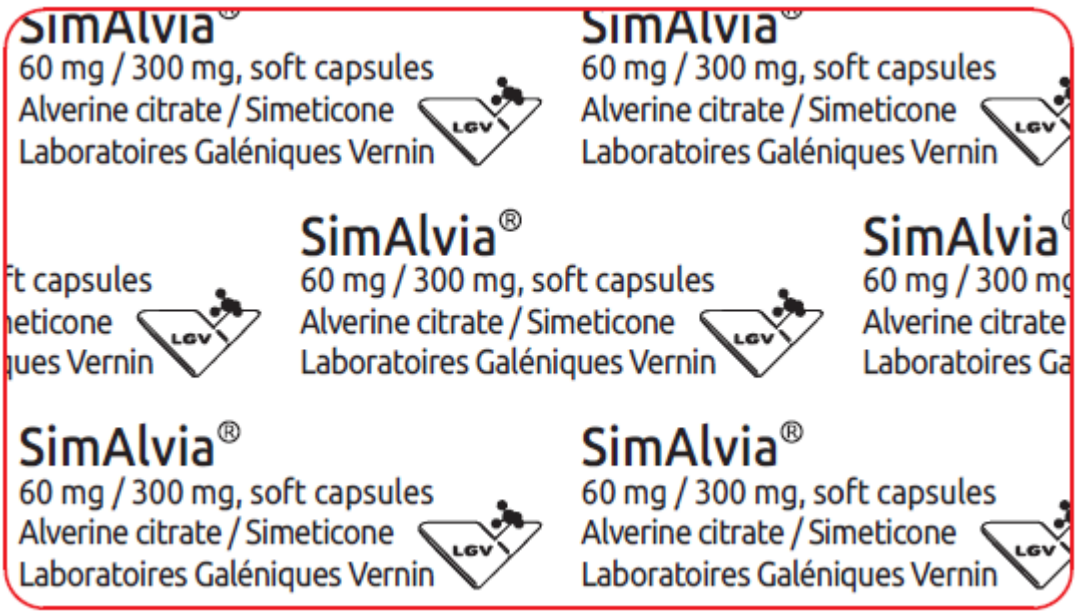

SimAlvia®
60 mg / 300 mg, soft capsules
Alverine citrate / Simeticone
Laboratoires Galéniques Vernin
LGV

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)