Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Alverine Citrate 60mg Hard Capsules
Alverine Citrate 120mg Hard Capsules

(alverine citrate)

UK Licence Numbers: PL 20117/0289-0290

Morningside Healthcare Ltd.

LAY SUMMARY

Alverine Citrate 60mg Hard Capsules
Alverine Citrate 120mg Hard Capsule**s**

This is a summary of the Public Assessment Report (PAR) for Alverine Citrate 60mg Hard Capsules (PL 20117/0289) and Alverine Citrate 120mg Hard Capsules (PL 20117/0290). It explains how Alverine Citrate 60mg and 120mg Hard Capsules were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Alverine Citrate 60mg and 120mg Hard Capsules.

The products will be collectively referred to as Alverine Citrate Hard Capsules throughout the remainder of this public assessment report (PAR).

For practical information about using Alverine Citrate Hard Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Alverine Citrate Hard Capsules and what are they used for?
Alverine Citrate Hard Capsules are 'generic medicines'. This means that Alverine Citrate Hard Capsules are similar to 'reference medicines' already authorised in the European Union (EU) called Spasmonal 60 mg and Spasmonal Forte 120 mg, hard capsules (Meda Pharmaceuticals Ltd, UK).

Alverine Citrate Hard Capsules are used to help people who have Irritable Bowel Syndrome (IBS), some of the symptoms of IBS are:

- Abdominal pains like cramp which come and go.
- Diarrhoea.
- Constipation.
- Feeling full and bloated.
- Wanting to go to the toilet urgently.

Sometimes these symptoms are worse if the patient is worried or under stress.

Alverine Citrate Hard Capsules can also be used for a condition of the large intestine called painful diverticular disease of the colon and to relieve period pains.

How do Alverine Citrate Hard Capsules work?
Alverine Citrate Hard Capsules contain the active ingredient alverine citrate. The product is an "anti-spasmodic" medicine that works by relaxing the muscles in the intestine (gut) and uterus (womb). This helps stop the pain the patient feels when the muscles become tense.

How are Alverine Citrate Hard Capsules used?
The pharmaceutical form of this medicine is a capsule and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as described in the package leaflet or as the patient's doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

The recommended dose is 1 or 2 capsules of 60mg or 1 capsule of 120mg taken up to 3 times a day.

Use in children: Alverine Citrate Hard Capsules are not suitable for children under 12 years old.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of

administration, and the duration of treatment.

For further information on how Alverine Citrate Hard Capsules are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can be obtained without a prescription.

What benefits of Alverine Citrate Hard Capsules have been shown in studies?
Because Alverine Citrate Hard Capsules are generic medicines, studies have been limited to tests to determine that they are bioequivalent to the reference medicines Spasmonal 60 mg and Spasmonal Forte 120 mg, hard capsules (Meda Pharmaceuticals Ltd, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Alverine Citrate Hard Capsules?
Because Alverine Citrate Hard Capsules are generic medicines and are bioequivalent to the reference medicines Spasmonal 60 mg and Spasmonal Forte 120 mg, hard capsules (Meda Pharmaceuticals Ltd, UK), their benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Alverine Citrate Hard Capsules, see section 4 of the package leaflet available on the MHRA website.

Why were Alverine Citrate Hard Capsules approved?
It was concluded that, in accordance with EU requirements, Alverine Citrate Hard Capsules have been shown to have comparable quality and to be bioequivalent to Spasmonal 60 mg and Spasmonal Forte 120 mg, hard capsules (Meda Pharmaceuticals Ltd, UK). Therefore, the MHRA decided that, as for Spasmonal 60 mg and Spasmonal Forte 120 mg, hard capsules (Meda Pharmaceuticals Ltd, UK); the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Alverine Citrate Hard Capsules?
A risk management plan (RMP) has been developed to ensure that Alverine Citrate Hard Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Alverine Citrate Hard 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/healthcare professionals will be monitored/reviewed continuously.

Other information about Alverine Citrate Hard Capsules
Marketing Authorisations were granted in the UK on 07 June 2017.

The full PAR for Alverine Citrate Hard Capsules follows this summary.

For more information about treatment with Alverine Citrate Hard Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2017.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Morningside Healthcare Ltd marketing authorisations for the medicinal products Alverine Citrate Hard Capsules (PL 20117/0289-0290) on 07 June 2017. The products are Pharmacy medicines (P) indicated in adults for the relief of smooth muscle spasm in conditions such as irritable bowel syndrome, painful diverticular disease of the colon and primary dysmenorrhoea.

The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Spasmonal 60 mg and Spasmonal Forte 120 mg, hard capsules which were originally authorised in the UK to Norgine Limited (PL 00322/5014R and PL 00322/0075) on 12 July 1990 and 09 October 1997 respectively. These reference licences underwent Change of Ownership procedures to the current marketing authorisation holder (MAH), Meda Pharmaceuticals Ltd (PL 15142/0240-0241) on 01 May 2011.

Alverine citrate is an antispasmodic with a direct action on smooth muscle. Alverine citrate is a spasmolytic, which has a specific action on the smooth muscle of the alimentary tract and uterus, without affecting the heart, blood vessels and tracheal muscle at therapeutic doses.

Two bioequivalence studies (conducted under fasting conditions) were submitted to support these applications. The applicant has stated that the bioequivalence studies were conducted in accordance with Good Clinical Practice (GCP) guidelines.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Alverine Citrate Hard Capsules outweigh the risks and Marketing Authorisations were granted.

II QUALITY ASPECTS

II.1 Introduction

Each capsule contains 60 mg or 120 mg of alverine citrate, as the active ingredient. Other ingredients consist of the pharmaceutical excipients maize starch, pregelatinised starch, magnesium stearate and:
Capsule shell components:
Body:
Indigo carmine (E 132), titanium dioxide (E 171) and gelatin.

Cap:
Iron oxide black (E 172), titanium dioxide (E 171) and gelatin.

Printing ink components:
Shellac (E 904), propylene glycol (E 1520), black iron oxide (E 172), and potassium hydroxide (E 525).

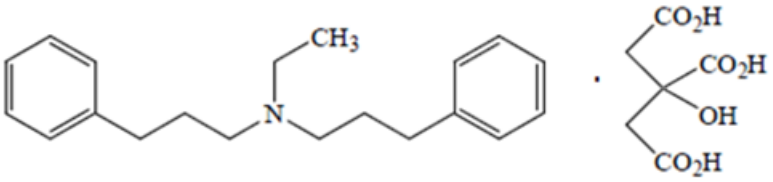
Both strengths of the finished product (60 mg and 120 mg) are packaged in polyvinyl chloride (PVC)/ polyvinylidene chloride (PVdC)-aluminium blisters in packs of 7, 10, 14, 28, 30, 56, 60, 84, 90, 100 and 112 capsules. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

INN: Alverine citrate
Chemical names: *N*-Ethyl-3-phenyl-*N*-(3-phenylpropyl)propan-1-amine dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

Structural formula:



Molecular formula: $C_{20}H_{27}N.C_6H_8O_7$
Molecular mass: 473.6
Appearance: White or almost white, crystalline powder.
Solubility: Slightly soluble in water and in methylene chloride, sparingly soluble in ethanol (96%).

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

Synthesis of the active 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.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

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

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

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

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious capsules containing 60 mg or 120 mg of alverine citrate per capsule, that are generic versions of the reference products Spasmonal 60 mg and Spasmonal Forte 120 mg, hard capsules (Meda Pharmaceuticals Ltd, UK). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the capsule shells which comply with a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that they are manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these products.

Manufacture of the products

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results. The process validation protocol to be followed for full-scale production batches has been provided and is satisfactory.

Finished Product Specifications

The finished product release and shelf life specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 21 months for the unopened blisters with the storage conditions ‘Do not store above 30ºC.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of alverine citrate are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Alverine Citrate Hard Capsules are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of alverine citrate is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of alverine citrate.

Based on the data provided, Alverine Citrate Hard Capsules can be considered bioequivalent to Spasmonal 60 mg and Spasmonal Forte 120 mg, hard capsules (Meda Pharmaceuticals Ltd, UK).

IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence studies:

STUDY 1

A randomised, open label, balanced, two-treatment, four period, two-sequence, single dose, fully replicated crossover, bioequivalence study of the applicant's test product Alverine Citrate 60mg Hard Capsules (Morningside Healthcare Ltd, UK) versus the reference product Spasmonal 60 mg, capsules (Meda Pharmaceuticals Ltd, UK) in healthy, adult, subjects under fasting conditions.
The applicant has provided an acceptable justification for the study design and dose administered.

Subjects were administered a single oral dose (2 x 60 mg capsules) of the test or reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

Table: Summary of pharmacokinetic data for alverine (geometric mean; ratio, CV%):

	Geometric mean		Ratio: Test/Reference (%)		CV%
Parameter	Test	Reference	Point estimate	90% CI	
AUC_{0-t}	4803.6015	4601.8170	104.3849%	97.2091 to 112.0904	33.8266%
C_{max}	858.0807	802.4473	106.9330%	97.1299 to 117.7255	46.4241%

Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data. Intra-subject coefficient of variation (%) for C_{max} was 46.7241

AUC_{0-t} area under the plasma concentration-time curve from zero to 72 hours
C_{max} maximum plasma concentration

The acceptance limits for AUC_{0-t} are 80.00 to125.00%. The acceptance limits for C_{max} will be widened if the intra-subject variability is more than 30%.

Non-compartmental pharmacokinetic analysis was performed on the observed drug concentrations in plasma of alverine and its metabolite monohydroxyl alverine (para hydroxy alverine) using a statistical package. The analysis of alverine and its metabolite monohydroxyl alverine was considered for statistical analysis and the analysis of alverine was considered for establishing bioequivalence.

Widening of acceptance limits for high variability is permissible when a replicate design is used (as is the case here). The widened acceptance range based on CV% of 46.7241 was 70.9164 to 141.011.

The Applicant reported a statistically significant sequence effect. The presence of significant sequence effect in a crossover trial is concerning as it is suggestive of a carryover effect. However, this is not of concern here as the plasma level at the start of each period was either 0 or less than 5% of C_{max}.

The confidence interval for AUC_{0-t} was contained within the acceptance range of 80.00 to 125.00%. The C_{max} acceptance limits were 70.9164 to 141.011 because of the high intra-subject variability (%CV=46.7241) and the confidence limits for C_{max} were within this range. However, widening of confidence limits for C_{max} was not needed as the confidence interval for C_{max} was also within the standard range of 80.00 to 125.00%. Therefore bioequivalence of Alverine Citrate 60 mg to Spasmonal 60 mg, after a single dose in a fasted state, has been demonstrated.

Study conclusion

The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for alverine lie within the acceptable limits of 80.00% to 125.00%, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product Alverine Citrate 60mg Hard Capsules (Morningside Healthcare Ltd, UK), is bioequivalent to the reference product Spasmonal 60 mg, capsules (Meda Pharmaceuticals Ltd, UK).

STUDY 2
A randomised, open label, balanced, two-treatment, four period, two-sequence, single dose, fully replicated crossover, bioequivalence study of the applicant's test product Alverine Citrate 120mg Hard Capsules (Morningside Healthcare Ltd, UK) versus the reference product Spasmonal Forte 120 mg, hard capsules (Meda Pharmaceuticals Ltd, UK) in healthy, adult, subjects under fasting conditions.

Subjects were administered a single oral dose (1 x 120 mg capsule) of the test or reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between dosing of Period-I to Period-II was 14 days, 10 days between dosing of Period-II to Period-III and 7 days between dosing of Period-III to Period-IV. The pharmacokinetic results are presented below:

Table: Summary of pharmacokinetic data for alverine (geometric mean; ratio, CV%):

	Geometric mean		Ratio: Test/Reference (%)		CV%
Parameter	Test	Reference	Point estimate	90% CI	
AUC_{0-t}	5872.7284	6047.3633	97.112	87.0436 to 108.3455	48.95
C_{max}	1055.026	1083.4477	97.3755	85.9820 to 110.2788	56.56

Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data. Intra-subject coefficient of variation (%) for C_{max} was 46.7241

AUC_{0-t} area under the plasma concentration-time curve from zero to 72 hours
C_{max} maximum plasma concentration

The acceptance limits for AUC_{0-t} are 80.00 to125.00%. The acceptance limits for C_{max} will be widened if the intra-subject variability is more than 30%.

Widening of acceptance limits for high variability is permissible when a replicate design is used (as is the case here). The widened acceptance range based on CV% of 46.7241 was 70.9164 to 141.011.

The confidence interval for AUC_{0-t} was contained within the acceptance range of 80.00-125.00%. The confidence interval for C_{max} was within the widened acceptance limits. However, widening of confidence limits for C_{max} was not needed as the confidence interval for C_{max} was also within the standard range of 80.00-125.00%. Therefore bioequivalence of Alverine Citrate 120mg Hard Capsules (Morningside Healthcare Ltd, UK) to Spasmonal Forte 120 mg, hard capsules (Meda Pharmaceuticals Ltd, UK), after a single dose in a fasted state, has been demonstrated.

Study conclusion
The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for alverine lie within the acceptable limits of 80.00% to 125.00%, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product Alverine Citrate 120mg Hard Capsules (Morningside Healthcare Ltd, UK) is bioequivalent to the reference product Spasmonal Forte 120 mg, hard capsules (Meda Pharmaceuticals Ltd, UK).

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Citrate Hard Capsules.

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

Summary of safety concerns	
Important identified risks	• Hypersensitivity to the active substance or to any of the excipients • Patients with paralytic ileus • Patients with intestinal obstruction
Important potential risks	• Hepatitis • Use in patients with difficulty or pain in passing urine • Use in patients with abnormal vaginal bleeding or discharge • Off label use
Missing information	• Use during pregnancy or lactation • Use in paediatric population

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications from a clinical viewpoint.

V User consultation

The package leaflet 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 language used for the purpose of user testing the PIL was English.

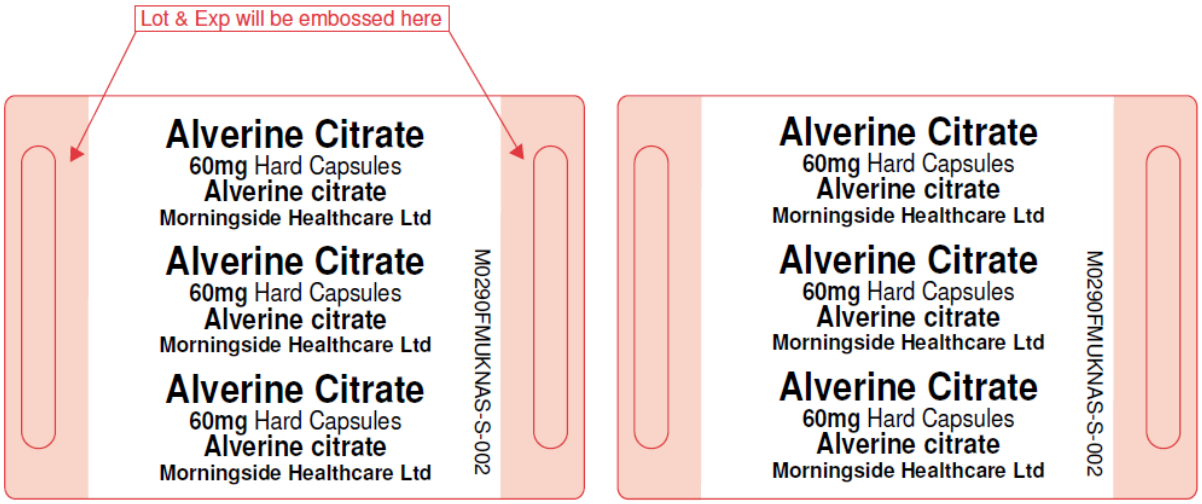
The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

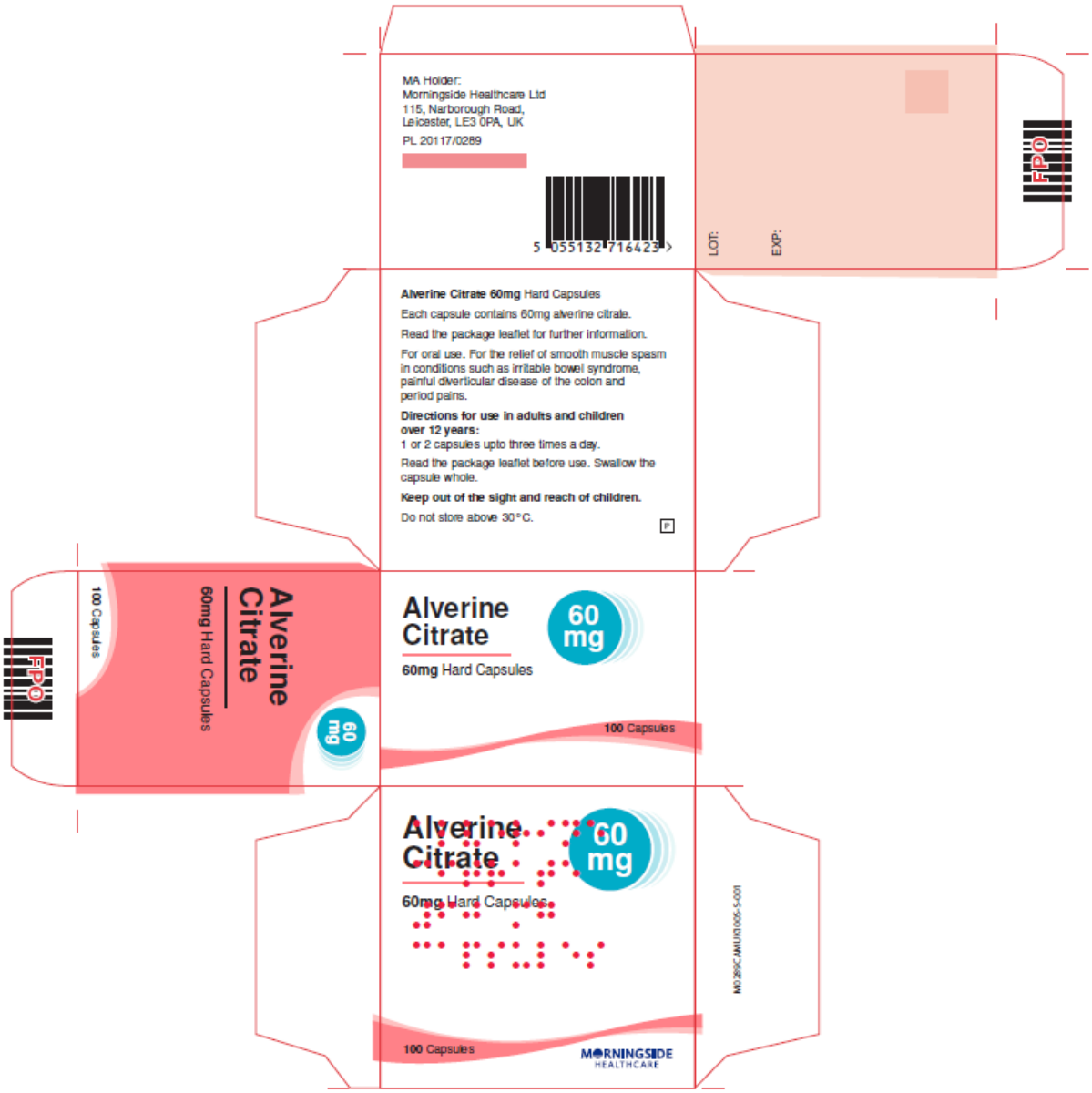
VI Overall conclusion, benefit/risk assessment and recommendation

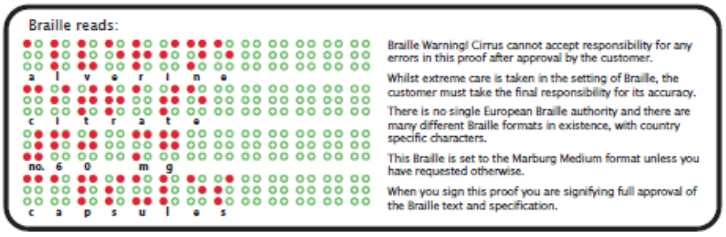
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with alverine citrate is considered to have demonstrated the therapeutic value of the compound. The products are bioequivalent to the marketed reference products and their risks and benefits are considered similar. The benefit-risk is, therefore, considered to be positive.

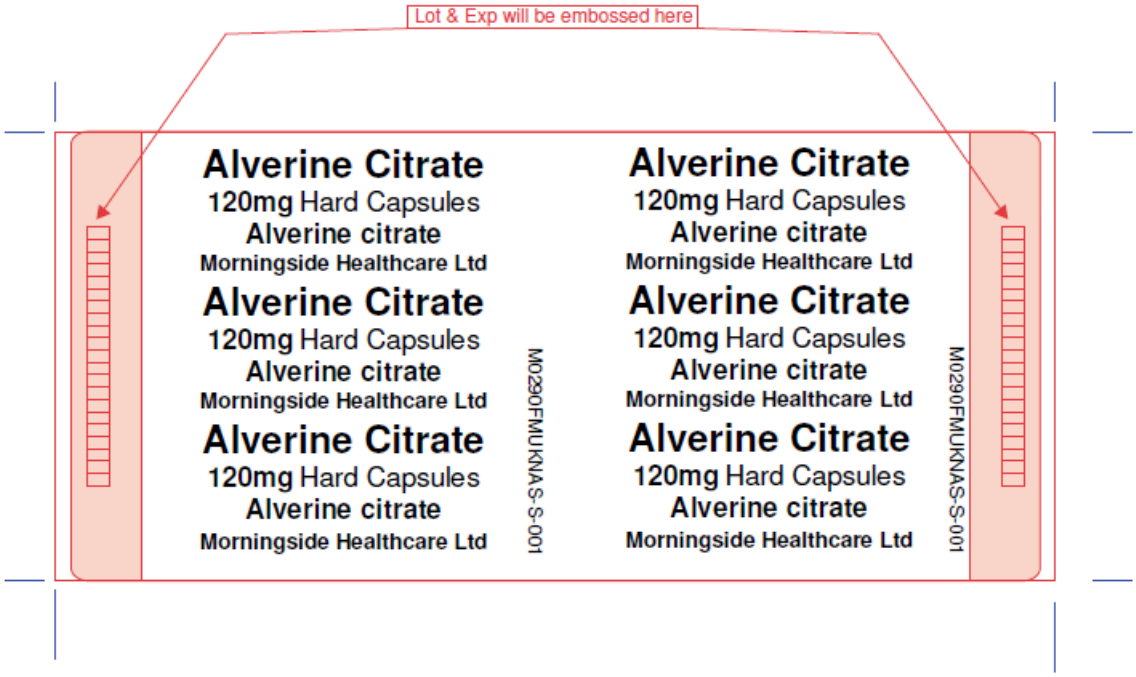
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the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

The approved labelling for this medicine is presented below:




MA Holder:
Morningside Healthcare Ltd
115, Narborough Road,
Leicester, LE3 0PA, UK
PL 20117/0289
5 055132 716423
LOT:
EXP:
Alverine Citrate 60mg Hard Capsules
Each capsule contains 60mg alverine citrate.
Read the package leaflet for further information.
For oral use. For the relief of smooth muscle spasm in conditions such as irritable bowel syndrome, painful diverticular disease of the colon and period pains.
Directions for use in adults and children over 12 years:
1 or 2 capsules upto three times a day.
Read the package leaflet before use. Swallow the capsule whole.
Keep out of the sight and reach of children.
Do not store above 30°C.
Alverine Citrate
60mg Hard Capsules
60 mg
100 Capsules
Alverine Citrate
60mg Hard Capsules
60 mg
100 Capsules
MORNINGSIDE HEALTHCARE
M/289/C/AMU/0005-S-001


Braille reads:
alverine
citrate
no. 60 mg
capsules
Braille Warning! Cirrus cannot accept responsibility for any errors in this proof after approval by the customer.
Whilst extreme care is taken in the setting of Braille, the customer must take the final responsibility for its accuracy.
There is no single European Braille authority and there are many different Braille formats in existence, with country specific characters.
This Braille is set to the Marburg Medium format unless you have requested otherwise.
When you sign this proof you are signifying full approval of the Braille text and specification.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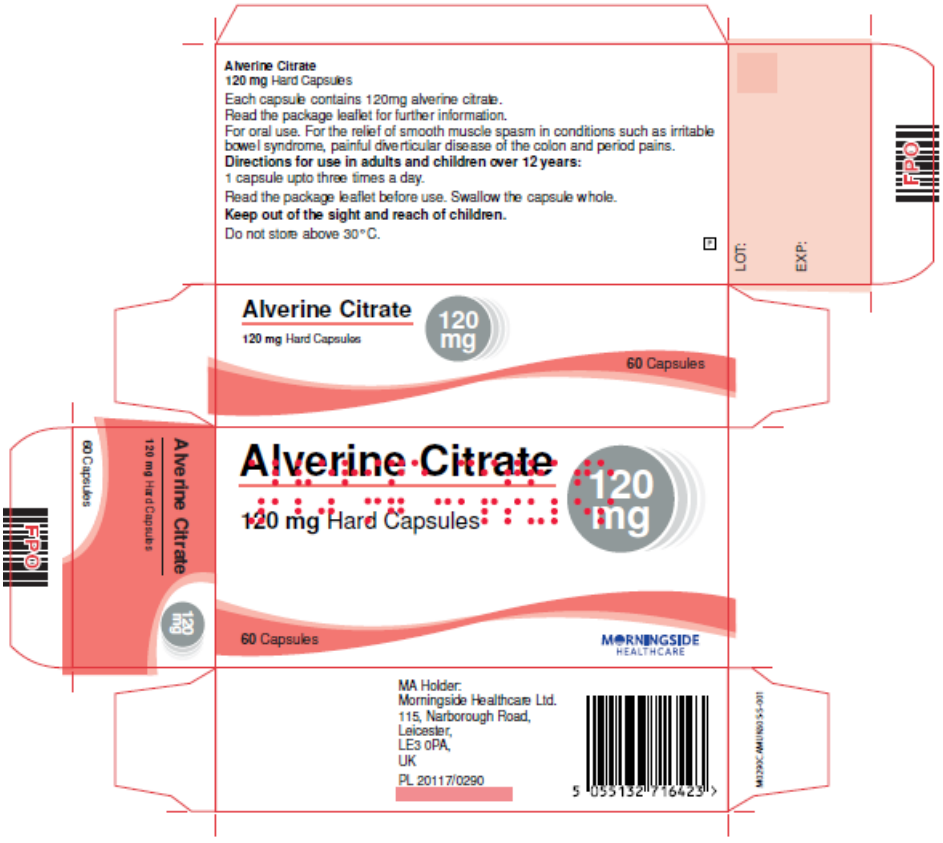
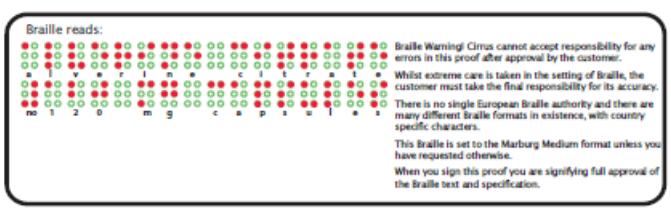
Alverine Citrate
120mg Hard Capsules
Alverine citrate
Morningside Healthcare Ltd
M0290FMUKNAS-S-001


Alverine Citrate
120 mg Hard Capsules
Each capsule contains 120mg alverine citrate.
Read the package leaflet for further information.
For oral use. For the relief of smooth muscle spasm in conditions such as irritable bowel syndrome, painful diverticular disease of the colon and period pains.
Directions for use in adults and children over 12 years:
1 capsule upto three times a day.
Read the package leaflet before use. Swallow the capsule whole.
Keep out of the sight and reach of children.
Do not store above 30°C.
LOT:
EXP:
Alverine Citrate
120 mg Hard Capsules
120 mg
60 Capsules
Alverine Citrate
120 mg Hard Capsules
60 Capsules
MORNINGSIDE HEALTHCARE
MA Holder:
Morningside Healthcare Ltd.
115, Narborough Road,
Leicester,
LE3 0PA,
UK
PL 20117/0290
5 055132 716423


Braille reads:
Alverine Citrate
no 120 mg capsules
Braille Warning! Cirrus cannot accept responsibility for any errors in this proof after approval by the customer.
Whilst extreme care is taken in the setting of Braille, the customer must take the final responsibility for its accuracy.
There is no single European Braille authority and there are many different Braille formats in existence, with country specific characters.
This Braille is set to the Marburg Medium format unless you have requested otherwise.
When you sign this proof you are signifying full approval of the Braille text and specification.

Annex 1

Table of content of the PAR update

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

Date submitted	Application type	Scope	Outcome