Public Assessment Report

Decentralised Procedure

ALVERINE CITRATE 60 MG HARD CAPSULES
GIELISM 60 MG HARD CAPSULES
(Alverine citrate)

Procedure No: UK/H/5206/001/DC and UK/H/5409/001/DC

UK Licence No: PL 28448/0012 and PL 28448/0026

Substipharm développement
This is a summary of the public assessment report (PAR) for Alverine citrate 60 mg hard capsules (PL 28448/0012; UK/H/5206/001/DC) and Gielism 60 mg hard capsules (PL 28448/0026; UK/H/5409/001/DC). It explains how Alverine citrate/Gielism 60 mg hard capsules were assessed and their authorisations recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Alverine citrate/Gielism 60 mg hard capsules.

For practical information about Alverine citrate/Gielism 60 mg hard capsules, patients should read the package leaflets or contact their doctor or pharmacist.

What are Alverine citrate/Gielism 60 mg hard capsules and what are they used for?

Alverine citrate/Gielism 60 mg hard capsules are ‘generic medicines’. This means that Alverine citrate 60/Gielism mg hard capsules are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Spasmonal 60 mg.

Alverine citrate/Gielism 60 mg hard capsules are used to

- help people who have irritable bowel syndrome (IBS). Some of the symptoms of IBS are:
  - abdominal pains like cramps which come and go
  - diarrhoea
  - constipation
  - feeling full and bloated
  - wanting to go to the toilet urgently
- treat a condition of the large intestine called painful diverticular disease of the colon
- relieve period pains.

How are Alverine citrate/Gielism 60 mg hard capsules used?

The active ingredient in these medicines is alverine citrate. These medicines can be obtained without a prescription. Alverine citrate/Gielism 60 mg hard capsules are intended for adults and adolescents over 12 years of age. The recommended dose is 1 or 2 capsules taken up to three times a day with a glass of water.

How do Alverine citrate/Gielism 60 mg hard capsules work?

Alverine citrate/Gielism 60 mg hard capsules belong to a group of medicines called anti-spasmodic medicines. They work by relaxing the muscles in the intestine (gut) and uterus (womb). This helps to stop the pain when muscles tense up.

How have Alverine citrate/Gielism 60 mg hard capsules been studied?

Alverine citrate/Gielism 60 mg hard capsules are generic medicines; studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Spasmonal 60 mg.
Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the benefits and risks of Alverine citrate/Gielism 60 mg hard capsules?**

Alverine citrate/Gielism 60 mg hard capsules are generic medicines and they are bioequivalent to the reference medicine. Therefore, their benefits and risks are taken as being the same as the reference medicine.

**Why are Alverine citrate/Gielism 60 mg hard capsules approved?**

It was concluded that, in accordance with EU requirements, Alverine citrate/Gielism 60 mg hard capsules are generic medicines and are bioequivalent to Spasmonal 60 mg. Therefore, the view was that, as for Spasmonal 60 mg, the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of Alverine citrate/Gielism 60 mg hard capsules?**

A risk management plan has been developed to ensure that Alverine citrate/Gielism 60 mg hard capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Alverine citrate/Gielism 60 mg hard capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Alverine citrate/Gielism 60 mg hard capsules**

The United Kingdom (UK) agreed to grant a Marketing Authorisation for Alverine citrate 60 mg hard capsules on 28 April 2014. After a subsequent national phase, a Marketing Authorisation was granted in the UK on 03 June 2014.

Ireland and the United Kingdom (UK) agreed to grant a Marketing Authorisation for Gielism 60 mg hard capsules on 28 April 2014. After a subsequent national phase, a Marketing Authorisation was granted in the UK on 03 June 2014.

The full PAR for Alverine citrate/Gielism 60 mg hard capsules follows this summary. For more information about treatment with Alverine citrate/Gielism 60 mg hard capsules, read the package leaflets or contact your doctor or pharmacist.

This summary was last updated in July 2014
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# Module 1
## Information about initial procedure

| **Product Names** | Alverine citrate 60 mg hard capsules  
Gielism 60 mg hard capsules |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Alverine citrate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Hard capsules</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>60 mg</td>
</tr>
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</table>
| **MA Holder** | Substipharm développement  
24 Rue Erlanger  
75016 Paris  
France |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Ireland (UK/H/5409/001/DC only) |
| **Procedure Numbers** | UK/H/5206/001/DC  
UK/H/5409/001/DC |
| **Timetable** | Day 210 – 28 April 2014 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
# Module 4

## Labelling

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON BOX**

### 1. NAME OF THE MEDICINAL PRODUCT

Alverine citrate 60 mg hard capsules  
Alverine citrate

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 60 mg of alverine citrate.

### 3. LIST OF EXCIPIENTS

### 4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.

- 3 capsules
- 10 capsules
- 12 capsules
- 20 capsules
- 30 capsules
- 60 capsules
- 90 capsules
- 100 capsules

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.  
Read the package leaflet before use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

EXP

### 9. SPECIAL STORAGE CONDITIONS
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER**

Substipharm développement
24 Rue Erlanger
75016 Paris
France

12. **MARKETING AUTHORIZATION NUMBER(S)**

PL 28448/0012

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

P

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Alverine citrate 60 mg hard capsules
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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<tbody>
<tr>
<td>PVC/Aluminum blister</td>
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<table>
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<td>Alverine citrate 60 mg hard capsules</td>
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<tr>
<td>Alverine citrate</td>
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</table>

<table>
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<th>4. BATCH NUMBER</th>
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<tr>
<th>5. OTHER</th>
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</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Gielism 60 mg hard capsules
Alverine citrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 60 mg of alverine citrate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.
3 capsules
10 capsules
12 capsules
20 capsules
30 capsules
60 capsules
90 capsules
100 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Substipharm développement
24 Rue Erlanger
75016 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

PL 28448/0026

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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<td>5. OTHER</td>
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Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that these applications for Alverine citrate 60 mg hard capsules (PL 28448/0012; UK/H/5206/001/DC) and Gielism 60 mg hard capsules (PL 28448/0026; UK/H/5409/001/DC) could be approved. These applications were submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS) for both procedures and Ireland as Concerned Member States (CMS) for Gielism 60 mg hard capsules. There were no Concerned Member States for Alverine citrate 60 mg hard capsules.

Alverine citrate/Gielism 60 mg hard capsules are pharmacy only products that can be obtained without a prescription (legal classification P).

These applications were made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Spasmonal 60 mg. Spasmonal 60 mg was originally granted a Marketing Authorisation to Norgine Limited on 12 July 1990 (PL 00322/5014R). Following a change of ownership, granted on 01 May 2011, the current Marketing Authorisation Holder is Meda Pharmaceuticals Limited (PL 15142/0240).

Alverine citrate/Gielism 60 mg hard capsules are spasmolytic and L-type calcium channel blockers, which have specific actions on the smooth muscle of the alimentary tract and uterus, without affecting the heart, blood vessels and tracheal muscle at therapeutic doses.

No new non-clinical studies were conducted, which is acceptable given that these applications were based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

With the exception of the bioequivalence study comparing the pharmacokinetics of alverine citrate with those of Spasmonal 60 mg (Norgine Limited), no new clinical studies were conducted. This is acceptable given that these applications were based on being generic medicinal products of an originator product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

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.

The RMS and CMSs considered that these applications could be approved at the end of procedure on 28 April 2014. After a subsequent national phase, Marketing Authorisations were granted in the UK on 03 June 2014.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Alverine citrate 60 mg hard capsules  
Gielism 60 mg hard capsules |
| Name(s) of the active substance(s) (INN) | Alverine Citrate |
| Pharmacotherapeutic classification (ATC code) | Other drugs for functional bowel disorders. (A03AX08) |
| Pharmaceutical form and strength(s) | Hard capsules, 60 mg |
| Reference numbers for the Decentralised Procedure | UK/H/5206/001/DC  
UK/H/5409/001/DC |
| Reference Member State | UK |
| Member States concerned | Ireland (UK/H/5409/001/DC only) |
| Marketing Authorisation Number(s) | PL 28448/0012  
PL 28448/0026 |
| Name and address of the authorisation holder | Substipharm développement  
24 Rue Erlanger  
75016 Paris  
France |
III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance – Alverine citrate

INN: Alverine citrate

Chemical name: 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_{20}H_{27}N \cdot C_6H_8O_7 (C_{26}H_{35}NO_7)

Molecular weight: 473.6 g/mol

Appearance: White to pale yellow fine powder

Solubility: slightly soluble in water and methylene dichloride. Sparingly soluble in ethanol.

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 specifications are provided for the active substance alverine citrate, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided that comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Satisfactory specifications have been provided for all packaging used for storing active alverine citrate. The primary packaging has been shown to comply with current legislation concerning materials in contact with foodstuff.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable. A suitable retest period has been set based on stability data submitted for the active substance stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the following pharmaceutical excipients:

Starch, pre-gelatinised and magnesium stearate.
The capsule shell contains gelatin and titanium dioxide (E171).
With the exception of the capsule shell all excipients used comply with their respective European Pharmacopoeia monographs. The capsule shell complies with an in-house specifications.

With the exception of gelatin none of the excipients contain materials of animal or human origin. Magnesium stearate, which can be derived from animals, was sourced from vegetable oil. No genetically modified organisms (GMO) have been used in the preparation of this product.

The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that it is manufactured in line with current European guidelines concerning minimising the risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

**Pharmaceutical Development**

The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the currently licensed product, Spasmonal 60 mg (Norgine Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference product.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on two commercial-scale batches of finished product. The results are satisfactory. A commitment has also been provided to perform process validation on the first three consecutive batches manufactured at commercial scale.

**Finished Product Specification**

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

**Container-Closure System**

The finished product is packaged in aluminium/polyvinylchloride blister packs of 3, 10, 12, 20, 30, 60, 90 or 100 capsules.

The Marketing Authorisation Holder has stated that these products are not intended for marketing. However, they have committed to providing the relevant licensing authority with the mock-ups for any pack size before marketing the products. 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 foodstuff.

**Stability of the product**

Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 3 years. These medicinal products do not require any special storage conditions.
Bioequivalence/bioavailability
A bioequivalence study was performed to compare the pharmacokinetics of the test product Alverine Citrate 60mg hard capsules versus the reference product Spasmonal 60 mg hard capsules.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PILs and labels are acceptable from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form
The MAA form is satisfactory from a pharmaceutical perspective.

Quality Overall Summary (Expert report)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of Marketing Authorisations is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of alverine citrate are well-known, no further non-clinical studies are required and none have been provided.

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

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

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

III.3 CLINICAL ASPECTS
Pharmacokinetics and Pharmacodynamics
With the exception of the following study, no new pharmacokinetic/pharmacodynamic data have been submitted with these applications and none are required.

In support of these applications, the Marketing Authorisation Holder has submitted the following bioequivalence study:

An open-label, randomised, two-sequence, four-period, controlled, randomised, replicate design, single dose study comparing the pharmacokinetics of the test product Alverine 60mg hard capsules versus the reference product Spasmonal 60 mg hard capsules in healthy adult subjects under fasting conditions.

The study was of an appropriate design and was conducted to the principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for the test and reference products.
Subjects were dosed orally with either the test or reference product following an overnight fast of at least 8 hours followed by a 6 hour fast post dose. Blood samples were taken pre- and up to 36 hours post dose. There was a washout period of 4 days between dosing.

A summary of the main pharmacokinetics results is presented in the table below:

<table>
<thead>
<tr>
<th>Test name</th>
<th>Parameter</th>
<th>Geo Mean Ratio (test/reference)</th>
<th>Lower 90 % CL</th>
<th>Upper 90 % CL</th>
<th>intra-subject CV %</th>
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</thead>
<tbody>
<tr>
<td>Classic 90 % Cl</td>
<td>AUC0-t</td>
<td>102.02</td>
<td>89.53</td>
<td>116.26</td>
<td>53.32</td>
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<tr>
<td>Classic 90 % Cl</td>
<td>Cmax</td>
<td>104.21</td>
<td>91.12</td>
<td>119.18</td>
<td>53.93</td>
</tr>
</tbody>
</table>

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

C_{max} maximum plasma concentration

The 90% confidence interval for the ratio of geometric means was within the pre-defined limits of 80.00-125.00% as specified in the Guideline on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). In conclusion, bioequivalence has been demonstrated between the test and reference products.

**Efficacy**

No new data on efficacy have been submitted and none are required for these types of applications.

**Safety**

With the exception of the data submitted during the bioequivalence studies, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

**SmPC, PIL and Labels**

The SmPCs, PILs and labels are acceptable from a clinical perspective.

**Pharmacovigilance System and Risk Management Plan**

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A risk management plan has been developed to ensure that Alverine citrate/Gielism 60 mg hard capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Alverine citrate/Gielism 60 mg hard capsules, including the appropriate precautions to be followed by healthcare professionals and patients.
Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Alverine citrate/Gielism 60 mg hard capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Alverine citrate/Gielism 60 mg hard capsules and the reference product.

No new or unexpected safety concerns arose from these applications.

The SmPCs, PILs and labels are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s product and the reference product. Extensive clinical experience with alverine citrate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
# Module 6

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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