

Public Assessment Report
Decentralised Procedure

Alverine Citrate 60mg & 120mg Capsules

UK/H/1361/001-002/DC

UK licence no: PL 20620/0037-8

NRIM Limited

LAY SUMMARY

On 30th September 2009, The Medicines Healthcare products Regulatory Agency (MHRA) granted NRI Limited Marketing Authorisations (licences) for the medicinal products Alverine Citrate 60mg Capsules and Alverine 120mg Capsules. These are pharmacy-only medicines (P).

Alverine citrate belongs to a group of medicines called “antispasmodic”. It works by relaxing the muscles in the intestine (gut) and uterus (womb). This helps to stop the pain when these muscles tense up. Alverine citrate capsules are used to help people who have Irritable Bowel Syndrome (IBS). The symptoms include tummy pains like cramp, diarrhoea, constipation, feeling full and bloated and wanting to go to the toilet urgently. Alverine Capsules are also used for a condition of the large intestine called painful diverticular disease of the colon. It is also used to relieve period pains.

The proposed products were considered to be generic versions of the reference products Spasmonal® 60mg Capsules (PL 00322/5014R) and Spasmonal Forte® 120mg Capsules (PL 00322/0075) which were first registered in UK in 1990 and 1997 respectively. Both products are authorised to Norgine Limited, UK as the marketing authorisation holder.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Alverine Citrate 60mg Capsules and Alverine Citrate 120mg Capsules outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Product Name	Alverine Citrate 60mg Capsules Alverine Citrate 120mg Capsules
Type of Application	Generic, Article 10.1
Active Substance	Alverine Citrate
Form	Capsules
Strength	60mg and 120mg
MA Holder	NRIM Limited, Marlborough House, 298 Regents Park Road, Finchley London N3 2UA UK
RMS	UK
CMS	Ireland
Procedure Number	UK/H/1361/001-002/DC
End of Procedure	24 th August 2009

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alverine citrate 60mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 60mg alverine citrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard (Capsule).

A Grey/Blue, size '3' hard gelatin capsules printed with 'NM' on cap and '60' on body, containing white to off white powder.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

The relief of smooth muscle spasm, in conditions such as irritable bowel syndrome, painful diverticular disease of the colon and primary dysmenorrhoea

4.2 Posology and method of administration

Recommended dose and dosage schedules:

Adults (including the elderly): 1 or 2 capsules one to three times daily.

Children below the age of 12 years: not recommended.

4.3 Contraindications

Paralytic ileus or known hypersensitivity to any of the ingredients.

Use during pregnancy and lactation.

4.4 Special warnings and precautions for use

Additional warnings to be included in the Patient Information Leaflet:

If this is the first time you have had these symptoms, consult your doctor before using any treatment.

If any of the following apply do not use Alverine Citrate Capsules; it may not be the right treatment for you. See your doctor as soon as possible if:

- you are aged 40 years or over
- you have passed blood from the bowel
- you are feeling sick or vomiting
- you have lost your appetite or lost weight
- you are looking pale and feeling tired
- you are suffering from severe constipation
- you have a fever
- you have recently travelled abroad
- you are or may be pregnant
- you have abnormal vaginal bleeding or discharge
- you have difficulty or pain passing urine.

Consult your doctor if you have developed new symptoms, or if your symptoms worsen, or if they do not improve after 2 weeks treatment.

4.5 Interaction with other medicinal products and other forms of interaction

None Stated.

4.6 Pregnancy and lactation

Although no teratogenic effects have been reported, use during pregnancy or lactation is not recommended as evidence of safety in preclinical studies is limited. Use is therefore contraindicated during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Possible side effects may include nausea, headache, dizziness, itching, rash, and allergic reactions. There have been isolated reports of jaundice due to hepatitis, which may have been immune-mediated; but this adverse reaction resolved on cessation of alverine treatment.

4.9 Overdose

Can produce hypotension and atropine-like toxic effects. Management is as for atropine poisoning with supportive therapy for hypotension.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

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.

5.2 Pharmacokinetic properties

After oral administration, alverine is rapidly converted to its primary active metabolite, which is then further converted to two 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.

5.3 Preclinical safety data

Preclinical studies provide evidence that alverine citrate has no significant systemic toxicity potential at the proposed dosage.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Maize Starch
Pregelatinised Starch (Starch 1500)
Magnesium Stearate
Capsule shell Cap
Gelatin
Black Iron Oxide
Titanium Dioxide

Capsule Shell Body

Gelatin
Brilliant Blue
Titanium Dioxide

Printing Ink Composition

Shellac
Dehydrated Alcohol
Isopropyl Alcohol
Butyl Alcohol
Propylene Glycol
Strong Ammonia Solution
Black Iron Oxide (E172)
Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original packaging.

6.5 Nature and contents of container

Tablets are packed in Al/PVC/PVdC blisters containing 3, 10, 12, 20, 90 or 100 capsules, in strips of 10 capsules as appropriate. Not all pack size will be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
NRIM Limited
Marlborough House
298, Regents Park Road
Finchley N3 2UA
London, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20620/0037

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/09/2009

10 DATE OF REVISION OF THE TEXT
30/09/2009

SUMMARY OF PRODUCT CHARACTERISTICS**1 NAME OF THE MEDICINAL PRODUCT**

Alverine citrate 120mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 120mg alverine citrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard (Caspule).

A Grey/Blue, size '1' hard gelatin capsules printed with 'NM' on cap and '120' on body, containing white to off white powder.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

The relief of smooth muscle spasm, in conditions such as irritable bowel syndrome, painful diverticular disease of the colon and primary dysmenorrhoea

4.2 Posology and method of administration

Recommended dose and dosage schedules:

Adults (including the elderly): 1 capsule one to three times daily.

Children below the age of 12 years: not recommended.

4.3 Contraindications

Paralytic ileus or known hypersensitivity to any of the ingredients.

Use during pregnancy and lactation.

4.4 Special warnings and precautions for use

Additional warnings to be included in the Patient Information Leaflet:

If this is the first time you have had these symptoms, consult your doctor before using any treatment.

If any of the following apply do not use Alverine Citrate Capsules; it may not be the right treatment for you. See your doctor as soon as possible if:

- you are aged 40 years or over
- you have passed blood from the bowel
- you are feeling sick or vomiting
- you have lost your appetite or lost weight
- you are looking pale and feeling tired
- you are suffering from severe constipation
- you have a fever
- you have recently travelled abroad
- you are or may be pregnant
- you have abnormal vaginal bleeding or discharge
- you have difficulty or pain passing urine.

Consult your doctor if you have developed new symptoms, or if your symptoms worsen, or if they do not improve after 2 weeks treatment.

4.5 Interaction with other medicinal products and other forms of interaction

None Stated.

4.6 Pregnancy and lactation

Although no teratogenic effects have been reported, use during pregnancy or lactation is not recommended as evidence of safety in preclinical studies is limited. Use is therefore contraindicated during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Possible side effects may include nausea, headache, dizziness, itching, rash, and allergic reactions including anaphylaxis.

There have been isolated reports of jaundice due to hepatitis, which may have been immune-mediated; but this adverse reaction resolved on cessation of alverine treatment.

4.9 Overdose

Can produce hypotension and atropine-like toxic effects. Management is as for atropine poisoning with supportive therapy for hypotension.

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5.1 Pharmacodynamic properties

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.

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6.1 List of excipients

Maize Starch

Pregelatinised Starch (Starch 1500)

Magnesium Stearate

Capsule shell Cap

Gelatin

Black Iron Oxide

Titanium Dioxide

Capsule Shell Body

Gelatin

Brilliant Blue

Titanium Dioxide

Printing Ink Composition

Shellac

Dehydrated Alcohol

Isopropyl Alcohol

Butyl Alcohol

Propylene Glycol

Strong Ammonia Solution

Black Iron Oxide (E172)

Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

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3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original packaging.

6.5 Nature and contents of container

Tablets are packed in Al/PVC/PVdC blisters containing 2, 10, 20, 30, 60 or 90 capsules, in strips of 10 capsules as appropriate. Not all pack sizes will be marketed.


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No special requirements.

- 7 MARKETING AUTHORISATION HOLDER**
NRIM Limited
Marlborough House
298, Regents Park Road
Finchley N3 2UA
London, United Kingdom
- 8 MARKETING AUTHORISATION NUMBER(S)**
PL 20620/0038
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
30/09/2009
- 10 DATE OF REVISION OF THE TEXT**
30/09/2009

Module 3

PRODUCT INFORMATION LEAFLET



NRIM

**ALVERINE CITRATE
60MG & 120MG CAPSULES**

PATIENT INFORMATION LEAFLET

**READ ALL OF THIS LEAFLET CAREFULLY
BECAUSE IT CONTAINS IMPORTANT
INFORMATION FOR YOU**

This medicine is available without prescription. However, you still need to take Alverine citrate capsules carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve after a few days.
- If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

THE LEAFLET CONTAINS INFORMATION ON:

- What Alverine citrate capsules are and what they are used for.
- Before you take Alverine citrate capsules
- How to take Alverine citrate capsules
- Possible side effects
- How to store Alverine citrate capsules
- Further information

1. WHAT ALVERINE CITRATE CAPSULES ARE AND WHAT THEY ARE USED FOR

Alverine citrate belongs to a group of medicines called 'antispasmodic'. It works by relaxing the muscles in the intestine (gut) and uterus (womb). This helps to stop the pain you feel when these muscles tense up.

Alverine citrate capsules are used to help people who have Irritable Bowel Syndrome (IBS). These are some of the symptoms of IBS:

- Tummy 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 you are worried or under stress.

Alverine citrate capsules are also used for a condition of the large intestine called painful diverticular disease of the colon. It is also used to relieve period pains.

Health tips for you

Try to make your everyday life a bit healthier:

- Allow plenty of time to do things, and avoid stress.
- Do not rush meals.
- Try to eat a balanced diet with high fibre foods.
- Do not eat foods, which seem to make your IBS worse

2. BEFORE YOU TAKE ALVERINE CITRATE CAPSULES

If this is the first time you have had these symptoms, consult your doctor before using any treatment.

Do not take Alverine citrate capsules if you:

- are allergic (hypersensitive) to Alverine citrate or any other ingredients in the capsules.
- have been told by your doctor that you have paralytic ileus.
- are aged 40 years or over
- have passed blood from the bowel
- are feeling sick or vomiting
- have lost your appetite or lost weight
- are looking pale and feeling tired
- are suffering from severe constipation
- have a fever
- have recently travelled abroad
- are or may be pregnant
- are breast feeding
- have abnormal vaginal bleeding or discharge
- have difficulty or pain passing urine.

Consult your doctor if any of the above applies to you as this may not be the right treatment for you.

Take special care with Alverine citrate capsules and consult your doctor if you:

- have developed new symptoms, or if your symptoms worsen, or if they do not improve after 2 weeks of treatment.

Taking other medicine

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription

Pregnancy and breast-feeding

The safety of alverine citrate for use during pregnancy and breast-feeding has not been established. Hence, it should be taken only if your doctor advises to do so. Please ask your doctor or pharmacist for advice before taking any medicine.

2. BEFORE YOU TAKE ALVERINE CITRATE CAPSULES

If this is the first time you have had these symptoms, consult your doctor before using any treatment.

Do not take Alverine citrate capsules if you:

- are allergic (hypersensitive) to Alverine citrate or any other ingredients in the capsules.
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- are suffering from severe constipation
- have a fever
- have recently travelled abroad
- are or may be pregnant
- are breast feeding
- have abnormal vaginal bleeding or discharge
- have difficulty or pain passing urine.

Consult your doctor if any of the above applies to you as this may not be the right treatment for you.

Take special care with Alverine citrate capsules and consult your doctor if you:

- have developed new symptoms, or if your symptoms worsen, or if they do not improve after 2 weeks of treatment.

Taking other medicine

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription

Pregnancy and breast-feeding

The safety of alverine citrate for use during pregnancy and breast-feeding has not been established. Hence, it should be taken only if your doctor advises to do so. Please ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Do not drive, operate machinery or do anything that requires you to be alert until you know how the capsules affect you.

3. HOW TO TAKE ALVERINE CITRATE CAPSULES

Follow your doctor's directions about when and how to take your tablets and look at the label on the carton. Your pharmacist will also help if you are not sure.

The usual dose is 1 or 2 capsules at a time. Take this dose up to 3 times a day.

Swallow your capsules without chewing them with a drink.

Children under 12 years old should not take Alverine citrate capsules.

If you take more Alverine citrate capsules than you should

It is important to stick to the dose on the label of the medicine. If you or someone else swallows several of these capsules all together, contact your doctor or nearest hospital emergency department immediately. Always take any capsules left over with you and also the box, as this will allow easier identification of the tablets.

If you forget to take Alverine citrate capsules

If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose do not take a double dose to make up for a forgotten dose, just carry on as before.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Alverine citrate capsules can have side effects although not everybody gets them.

Stop taking Alverine citrate capsules and tell your doctor immediately if you experience:

- Yellowing of the whites of the eyes and skin. This could be an inflammation of the liver and may occur very rarely.

Tell your doctor if you experience:

- A rash or feel unwell. This may be an allergic reaction to Alverine citrate capsules and may occur occasionally.

The following side effects have been reported rarely:

- feeling of sickness,
- dizziness,
- headache,
- allergy,
- rash or itching.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ALVERINE CITRATE CAPSULES

- Keep out of the reach and sight of children.
- Do not use Alverine citrate capsules after the expiry date, which is stated on the blister and carton. The expiry date refers to the last day of the month.
- Do not store above 25°C. Store in the original packaging.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION**What Alverine citrate capsules contain**

The name of your medicine is Alverine citrate 60mg & 120mg capsules.

The active substance in your capsule is alverine citrate. Each capsule contains 60mg or 120mg of alverine citrate. This is the ingredient that makes Alverine citrate capsules work. Other ingredients are maize starch, pregelatinized starch (Starch 1500), magnesium stearate, gelatin, black iron oxide, brilliant blue and titanium dioxide.

What Alverine citrate capsules look like and contents of the pack

Alverine citrate 60mg capsules are grey/blue, hard, gelatin capsules printed with 'NM' on cap and '60' on body, containing a white to off white powder. Alverine citrate 120mg capsules are grey/blue, hard, gelatin capsules printed with 'NM' on cap and '120' on body, containing a white to off white powder.

Alverine citrate 60mg and 120mg capsules are supplied in blisters containing 3, 10, 12, 20, 30, 60, 90 or 100 capsules, in strips of 10 capsules as appropriate. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

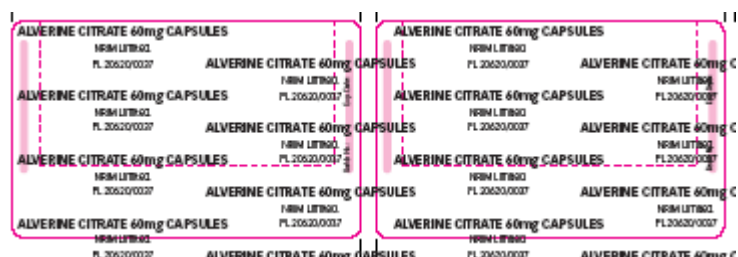
The Marketing Authorisation holder and manufacturer of these capsules is NRIM Limited, Marlborough House, 298 Regents Park Road, Finchley, London, N3 2UA, United Kingdom

This leaflet was prepared in 11/2008

Module 4

Labelling

Carton

**Label**

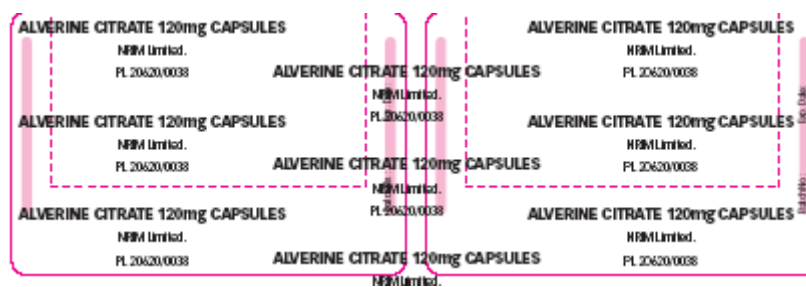
Carton



Carton



Label



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Alverine citrate 60mg & 120mg Capsules, in the treatment of: relief of smooth muscle spasm, in conditions such as irritable bowel syndrome, painful diverticular disease of the colon and primary dysmenorrhea, is approvable.

These are applications 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 the original, Spasmonal® 60mg Capsules (PL 00322/5014R) and Spasmonal Forte® 120mg Capsules (PL 00322/0075) were first registered in UK in 1990 and 1997 respectively. Both products are authorised to Norgine Limited, UK as the marketing authorisation holder.

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. After oral administration, alverine is rapidly converted to its primary active metabolite, which is then further converted to two secondary metabolites.

The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements.

A formal *Environmental Risk Assessment* has not been performed as the product is intended for generic substitution. Hence no increase in environmental risk is to be expected compared to that of the reference product.

No *Risk Management Plan* other than documentation of pharmacovigilance system has been provided. For generics this is acceptable, since the innovator product is not subject to specific risk management measures.

User Consultation: The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL 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.

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly 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. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information'

issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Alverine Citrate 60mg Capsules Alverine Citrate 120mg Capsules
Name(s) of the active substance(s) (INN)	Alverine Citrate
Pharmacotherapeutic classification (ATC code)	Other drugs for functional bowel disorders A03 A X 08
Pharmaceutical form and strength(s)	Capsules; 60mg & 120mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1361/001-002/DC
Reference Member State	United Kingdom
Member States concerned	Ireland
Marketing Authorisation Number(s)	PL 20620/0037-38
Name and address of the authorisation holder	NRIM Limited Marlborough House 298, Regents Park Road Finchley N3 2UA London, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

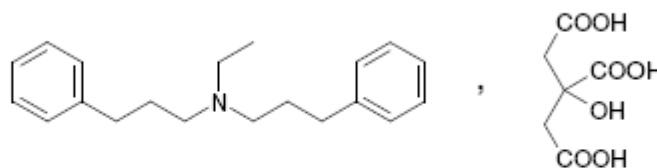
Alverine citrate

rINN:	Alverine citrate
Compendial name:	Alverine citrate (Ph.Eur.)
Chemical name(s):	<i>N</i> -ethyl-3-phenyl- <i>N</i> -(3-phenylpropyl)propan-1-amine dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate <i>N</i> -ethyl- <i>N</i> -(3-phenylpropyl)-benzenepropanamine, citrate.
Other name(s);	<i>N,N</i> -bis(phenyl-3-propyl)-ethylamine citrate <i>N</i> -ethyl-3,3'-diphenyl-dipropylamine, citrate.
CAS number:	5560-59-8

3.2.S.1.2 Structure

3.2.S.1.2 Structure

Chemical structure :



Molecular formula : $C_{20}H_{27}N \cdot C_6H_8O_7$ ($C_{26}H_{35}NO_7$)

Molecular weight : $473.6 \text{ g} \cdot \text{mol}^{-1}$

Chirality : Not applicable

3.2.S.1.3 General Properties

Description:	White to pale yellow fine powder
Solubility:	Slightly soluble in water and methylene dichloride. Sparingly soluble in ethanol.
Melting point:	About 104°C
Polymorphism:	No polymorphism has been found.

Manufacture

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance alverine citrate

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate on-process controls and intermediate specifications and applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

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

An appropriate specification is provided for the active substance alverine citrate, with suitable test methods and limits. The drug substance is described in a monograph of the European Pharmacopoeia. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Suitable certificates of analysis have been provided for all reference standards used.

Satisfactory specifications and certificates have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug and supports an appropriate re-test period.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely maize starch, pregelatinised starch and magnesium stearate. All ingredients within the capsule comply with their relevant Ph Eur monographs.

The capsule shell cap contains: gelatin, black iron oxide and titanium dioxide. The capsule shell body contains: gelatin, brilliant blue and titanium dioxide. The printing ink consists of: shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide(E172) and potassium hydroxide.

In the absence of Ph Eur monographs the ingredients that comprise the capsule shell cap and body comply with in-house specifications. The ingredients within the printing ink shellac, butyl alcohol, strong ammonia solution and potassium hydroxide are controlled to the National Formulary (NF). The remaining ingredients dehydrated alcohol; isopropyl alcohol and propylene glycol are controlled to the US Pharmacopoeia (USP).

Appropriate justification for the inclusion of each excipient has been provided.

Satisfactory certificates of Analysis have been provided for all excipients.

Dissolution and Impurity profiles

Dissolution and impurity profiles for all strengths of drug product were found to be similar to those for the reference products.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory validation batch data on each strength have been provided.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data

from two batches of each strength of drug product have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System

Product is packaged in blisters composed of aluminium/polyvinylchloride/polyvinylidene chloride (Al/PVC/PVdC). Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 2,10,20,30,60 or 90 capsules. Not all pack sizes will be marketed. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are “Do not store above 25°C” and “Store in original package”.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

III.2 PRE-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of alverine citrate are well known. As alverine citrate is a widely-used, well-known active substance, no further studies are required and the applicant has not provided any. An overview based on a literature review is, thus, appropriate.

The non-clinical overview has been written by a pharmaceutical and non-clinical consultant with experience of regulatory affairs and pharmacovigilance.

The Non-clinical Overview contains a review of 4 references up to 2007 and was dated the 5th of February 2008.

The non-clinical overview was very brief, but it is accepted that there is little non-clinical data on alverine citrate in the public domain. No data were found that would alter the risk-benefit analysis for alverine citrate.

III.3 CLINICAL ASPECTS

The applicant has submitted two bioequivalence studies performed under fasting conditions. Both were randomized, single dose, two treatment, two sequence, crossover, bioequivalence study of test product, Alverine Citrate NRIM (60mg or 120 mg) Capsules and reference product, Spasmonal (60mg or 120mg) Capsules (Norgine, UK, Ltd) in healthy subjects.

60mg Dose Study

This was a randomized, single dose, two treatment, two sequence, crossover, bioequivalence study of test product, Alverine Citrate NRIM 60mg Capsules and reference product, Spasmonal 60mg Capsules (Norgine, UK, Ltd) in healthy subjects under fasting conditions.

Healthy subjects were enrolled into the study. Blood samples were collected at frequent intervals up to 96 hours post dosing. There was a 10 day wash out period.

A full description of the statistical methods used has been provided in the study report.

The main pharmacokinetic parameters, for the parent drug, Alverine Citrate and its major metabolite, Mono-hydroxyl alverine, are summarised in the tables 1 & 2 below.

Table 1 Summary of the main pharmacokinetic parameters of Alverine Citrate 60mg

Parameter	Test product (Mean±SD)	Ref. product (Mean±SD)	90% CI
C_{max} (ng/mL)	0.566 ± 0.663	0.524 ± 0.443	84.10 – 111.27
T_{max} (hr)	1.016 ± 0.590	0.986 ± 0.532	
T_{1/2} (hr)	3.933 ± 3.424	3.697 ± 2.248	
AUC_{0-t} (ng/hr/mL)	1.804 ± 2.322	1.864 ± 2.022	83.13 – 110.26
AUC_{0-∞}(ng/hr/mL)	2.251 ± 2.452	2.338 ± 2.235	85.74 – 110.29

Table 2 Summary of the main pharmacokinetic parameters of Monohydroxyl Alverine

Parameter	Test product (Mean±SD)	Ref. product (Mean±SD)	90% CI
C_{max} (ng/mL)	4.296 ± 4.546	4.417 ± 5.797	89.10 – 113.47
T_{max} (hr)	4.129 ± 7.336	2.967 ± 3.863	
T_{1/2} (hr)	44.811± 41.793	40.659± 44.778	
AUC_{0-t} (ng/hr/mL)	86.786 ± 90.311	78.343 ± 79.292	97.30 – 123.92
AUC_{0-∞}(ng/hr/mL)	101.590 ± 90.878	102.530 ± 131.691	93.99 – 121.12

Three adverse events were reported (1 diarrhoea, 2 headaches) which were assessed as non-serious. No serious adverse events were reported.

120mg Dose Study

This was a randomized, single dose, two treatment, two sequence, crossover, bioequivalence study of test product, Alverine Citrate NRIM 120mg Capsules and reference product, Spasmonal 120mg Capsules (Norgine, UK, Ltd) in healthy subjects under fasting conditions.

ANOVA was performed on log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} and 90% confidence interval were constructed for the ratio of geometric least square mean of the Test and Reference products, obtained from the log-transformed data.

Bioequivalence was concluded if the 90% confidence interval for the test/reference ratio falls within the acceptable range of 75.00% to 133.00% for C_{max} and 80.00% to 125.00% for AUC_{0-t} and AUC_{0-inf}.

The main pharmacokinetic parameters, for the parent drug, Alverine Citrate and its major metabolite, Mono-hydroxyl alverine, are summarised in the tables 3 & 4 below.

Table 3 Summary of the main pharmacokinetic parameters of Alverine Citrate 120mg

Parameter	Test product (Mean±SD)	Ref. product (Mean±SD)	90% CI
C_{max} (ng/mL)	3.7856 ± 13.3492	3.6410 ± 10.2268	0.0845 – 0.1079
T_{max} (hr)	1.0 ± 0.33	1.04 ± 0.46	
T_{1/2} (hr)	2.85± 1.61	3.02 ± 2.72	
AUC_{0-t} (ng/hr/mL)	17.4139 ± 95.6607	18.6636 ± 97.3227	0.0843 – 0.1039
AUC_{0-∞}(ng/hr/mL)	18.3733 ± 96.4731	20.3666 ± 104.5627	0.0872 – 0.1055

Table 4 Summary of the main pharmacokinetic parameters of Monohydroxyl Alverine

Parameter	Test product (Mean±SD)	Ref. product (Mean±SD)	90% CI
C_{max} (ng/mL)	6.9395 ± 5.5161	7.0397 ± 5.2261	0.0888 – 0.1103
T_{max} (hr)	1.38 ± 0.39	1.43 ± 0.52	
T_{1/2} (hr)	6.25± 2.93	6.26± 2.77	
AUC_{0-t} (ng/hr/mL)	27.4827 ± 23.9097	26.4636 ± 21.1121	0.0957 – 0.1107
AUC_{0-∞}(ng/hr/mL)	29.6824 ± 25.0075	28.4335 ± 21.6380	0.0963 – 0.1108

No serious adverse events were reported.

Conclusion

The application concerns two dosage strengths, 60 mg and 120 mg. Both bioequivalence studies demonstrate bioequivalence, with the 90% CI for C_{max} and AUC within the 0.80-1.25 acceptance criterion.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**QUALITY**

The important quality characteristics of Alverine Citrate 60mg & 120mg 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.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Alverine Citrate 60mg & 120mg Capsules and Spasmonal® 60mg Capsules (PL 00322/5014R) and Spasmonal Forte® 120mg Capsules (PL 00322/0075).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical 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 risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome