# SILAMARIE

## THR 15817/0009

## UKPAR

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SILAMARIE

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bio-Health Limited a Traditional Herbal Registration Certificate for the traditional herbal medicinal product SILAMARIE (Traditional Herbal Registration number: THR 15817/0009) on 13 December 2011. This product is available without prescription and can be bought from pharmacies and other outlets.

SILAMARIE is a traditional herbal medicinal product used to relieve the symptoms associated with occasional over indulgence of food and drink such as indigestion and upset stomach, based on traditional use only. The active ingredient in SILAMARIE comes from the fruit of the Milk thistle plant (Silybum marianum (L.) Gaertner).

This registration is based exclusively upon the longstanding use of Milk thistle fruit as a traditional herbal medicine and not upon data generated from clinical trials. There is no requirement under the Traditional Herbal Registration Scheme to prove scientifically that a product works.

No new or unexpected safety concerns arose from this application and it was, therefore, decided that a Traditional Herbal Registration Certificate could be granted.
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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal medicinal product SILAMARIE (THR 15817/0009) to Bio-Health Limited on 13 December 2011. This product is on the general sales list (GSL).

This application was submitted according to Article 16.c of Directive 2001/83 EC, as amended, as part of the Traditional Herbal Medicines Registration Scheme. The product is used to relieve the symptoms associated with occasional over indulgence of food and drink, such as indigestion and upset stomach, based on traditional use only.

The data supplied by the applicant demonstrate 30 years of traditional use of Milk thistle fruit in the EU. A satisfactory review of the available safety data on Milk thistle fruit has also been provided, together with an Expert Safety Report supporting the proposed product.
HERBAL SUBSTANCE: MILK THISTLE FRUIT
Latin name of plant: Silybum marianum (L.) Gaertner
Plant family: Asteraceae

Manufacture of the Herbal Substance
The plants are cultivated in Poland and the ripe fruit is harvested in July or August. Following harvest, the fruit is dried.

The herbal substance is cultivated under GACP controlled conditions. Pesticides are not used during cultivation and assurance has been provided from the supplier that fumigant treatments/irradiation has not been used on the plant.

Control of the Herbal Substance
The specifications for the herbal substance are in line with the Ph Eur monograph for Milk thistle fruit and are satisfactory.

Certificates of Analysis are presented for batches of the herbal substance, giving full results for test parameters to support the proposed specification.

Container Closure System
The herbal substance is not stored, therefore, no information is provided.

Stability of the Herbal Substance
No stability data have been provided and none are needed due to the short time between harvest and manufacture of the herbal product.

HERBAL PREPARATION: POWDERED MILK THISTLE FRUIT
The herbal preparation consists simply of the powdered herbal substance; this is produced prior to filling into the capsules as part of the herbal substance manufacturing process. The herbal preparation is not stored.

HERBAL PRODUCT: SILAMARIE

Description and Composition of the Herbal Product
The product is presented as a clear, hypromellose, hard capsule containing 450 mg of powdered Milk thistle fruit.

The compatibility of the herbal preparation with the hypromellose is demonstrated by the stability testing results. The hypromellose is controlled in line with the Ph Eur monograph.

Manufacture of the Herbal Product
A flow diagram outlining the various stages of the manufacturing process and the in-process controls is provided.
In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on product batches and the results are satisfactory.

**Control of Herbal Product**
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 have been provided and comply with the release specification.

**Container Closure System**
The capsules are stored in either a Duma 110ml HDPE plastic container with a tamper evident threaded Duma cap (60 capsule pack) or a Duma 200ml HDPE plastic container with a tamper evident Duma cap (120 capsule pack).

Suitable specifications have been provided by the packaging suppliers and it has been confirmed that all primary packaging materials comply with current legislation relating to plastic materials and articles intended to come into contact with foodstuffs.

**Stability of the Herbal Product**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a product shelf-life of 2 years is appropriate when the storage precautions ‘Do not store above 25°C’ and ‘Store in the original package’ are applied.

**Pharmaceutical Expert**
The Quality Overall Summary has been written by a pharmacist with suitable expertise.

**Summary of Product Characteristics, Labels and Patient Information Leaflet**
All product literature is satisfactory.

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. 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.

**CONCLUSION**
There are no objections to granting of a Traditional Herbal Registration from a quality point of view.
NON-CLINICAL ASSESSMENT

NON-CLINICAL OVERVIEW
An Expert Safety Report was provided, which included reviews of some non-clinical data. The Expert Safety Report was written by a suitably qualified professional.

Due to a shortage of published data on Milk thistle fruit it is not possible to assess if the safety package for the phytochemical constituents of Milk thistle fruit is acceptable to the standards of today’s GLP and safety testing requirements. However, the information supplied demonstrating traditional use is acceptable and, thus, the lack of provision of a complete standard safety package may be acceptable and in compliance with guideline EMEA/HMPC/32116/05.

Assurance has been given that the results of genotoxicity testing will be provided before the renewal date of the Traditional Herbal Registration.

The overview submitted in support of this application is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The SmPC for this product is satisfactory from a non-clinical point of view.

ENVIRONMENTAL RISK ASSESSMENT
An environmental risk assessment is not required for herbal medicinal products according to guidance CPMP/SWP/4447/00.

CONCLUSION
There are no objections to granting of a Traditional Herbal Registration from a non-clinical point of view.
INDICATION
The applicant has proposed the following therapeutic indication:

‘SILAMARIE is a traditional herbal medicinal product used to relieve the symptoms associated with occasional over indulgence of food and drink, such as indigestion and upset stomach, based on traditional use only.’

The indication is acceptable.

POSOLOGY AND METHOD OF ADMINISTRATION
The applicant has proposed the following posology:

‘For oral use only.
Adults and the elderly.
Take 1 or 2 capsules 3 times daily swallowed with water up to a maximum of 6 capsules daily.
Duration of use:-
If the condition worsens or symptoms persist, a doctor or a qualified healthcare practitioner should be consulted.
This product is not recommended for children or adolescents under 18 years of age (see Section 4.4 Special Warnings and Precautions for Use).’

This is acceptable.

EFFICACY
No clinical efficacy data is required for registration of Traditional Herbal Medicinal Products.

EVIDENCE OF TRADITIONAL USE
Article 16 c 1 (c) requires the applicant to provide bibliographic or expert evidence to show that the medicinal product in question, or a corresponding product, has been in medicinal use throughout a period of at least 30 years, including at least 15 years within the EU.

The applicant has provided a bibliographic review as evidence of the use of Milk thistle fruit within the EU for a period exceeding 30 years.

The information provided is considered to satisfy the requirement to demonstrate use for at least 30 years, of which at least 15 years have been in an EU Member State. The requirements of the Directive are, therefore, addressed for this aspect.

SAFETY REVIEW
Article 16 c 1 (d) requires the applicant to provide a bibliography of the safety data together with an Expert Safety Report.

A safety review has been provided as well as an Expert Safety Report written by a suitably qualified professional. These are satisfactory.
PRODUCT LITERATURE
The SmPC, PIL and labelling for this product are medically satisfactory.

CONCLUSION
There are no objections to granting of a Traditional Herbal Registration from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT: RISK ASSESSMENT

QUALITY
The quality data submitted with this application are satisfactory.

NON-CLINICAL
No new non-clinical data were submitted with this application. The results of genotoxicity testing will be provided before the Traditional Herbal Registration is renewed.

EFFICACY AND SAFETY
No clinical efficacy data are required for registration of Traditional Herbal Medicinal Products. The applicant has provided a bibliographic review which shows ample evidence for the use of Milk thistle fruit within the EU for a period exceeding 30 years.

A satisfactory review of the safety data has also been provided.

The SmPC, PIL and labelling are satisfactory.

BENEFIT: RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The benefit: risk balance is acceptable and a Traditional Herbal Registration may be granted.
SILAMARIE

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STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Traditional Herbal Registration application on 28 January 2011

2. Following standard checks and communication with the applicant the MHRA considered the application valid on 21 February 2011

3. Following assessment of the application the MHRA requested further information relating to the clinical dossier on 17 March 2011 and the quality dossier on 28 July 2011

4. The applicant responded to the MHRA’s requests, providing further information on the clinical and quality dossiers on 18 August 2011

5. Following assessment of the response the MHRA requested further information relating to the quality dossier on 30 September 2011

6. The applicant responded to the MHRA’s request, providing further information on the quality dossier on 29 November 2011

7. A THR was granted on 13 December 2011
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
SILAMARIE

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each hard capsule contains 450mg of Milk Thistle fruits (*Silybum marianum* L. Gaertner)
For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Hard capsules.
Clear size 0 hard capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
SILAMARIE is a traditional herbal medicinal product used to relieve the symptoms associated with occasional over indulgence of food and drink, such as indigestion and upset stomach, based on traditional use only.

4.2 Posology and method of administration
For oral use only.
Adults and the elderly.
Take 1 or 2 capsules 3 times daily swallowed with water up to a maximum of 6 capsules daily.
Duration of use:-
If the condition worsens or symptoms persist, a doctor or a qualified healthcare practitioner should be consulted.
This product is not recommended for children or adolescents under 18 years of age (see Section 4.4 Special Warnings and Precautions for Use).

4.3 Contraindications
Hypersensitivity to Milk Thistle or other members of the Asteraceae (Compositae) family or any of the excipients.

4.4 Special warnings and precautions for use
Do not exceed the stated dose.
The use of this product is not recommended in children and adolescents below the age of 18 years as there is no relevant indication.
Patients suffering from active liver disease should consult their doctor before taking the product.
Milk Thistle may alter the way that certain drugs are broken down by the liver (see Section 4.5 Interaction with other medicinal products and other forms of medicine).
If the condition worsens, or symptoms persist, a doctor or qualified healthcare practitioner should be consulted.

4.5 **Interaction with other medicinal products and other forms of interaction**

*In vitro*, Milk Thistle extract resulted in inhibition of CYP isoenzymes. However, the clinical relevance of these findings is not established.

4.6 **Fertility, pregnancy and lactation**

The safety of SILAMARIE during pregnancy and lactation has not been established. Due to the lack of sufficient data, use during pregnancy and lactation is not recommended. Studies on fertility have not been carried out.

4.7 **Effects on ability to drive and use machines**

No studies on the effect on the ability to drive and use machines have been performed.

4.8 **Undesirable effects**

Gastrointestinal reactions (nausea, upset stomach, diarrhoea), headache, allergic reactions (urticaria, skin rash, pruritis, analphylaxis). The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a qualified healthcare practitioner should be consulted.

4.9 **Overdose**

No case of overdose has been reported. Supportive and symptomatic treatment should be provided as appropriate.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

5.2 **Pharmacokinetic properties**

Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

5.3 **Preclinical safety data**

Test on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Hypromellose (capsule shell)
6.2 **Incompatibilities**
Not Applicable.

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
Store below 25°C
Store in the original container.

6.5 **Nature and contents of container**
Duma 110ml HDPE plastic container and tamper evident threaded Duma cap.
Duma 200ml HDPE plastic container and tamper evident Duma cap.
SILAMARIE pack contains 60 or 120 Capsules.

6.6 **Special precautions for disposal**
There are no special precautions for disposal.

7 **MARKETING AUTHORISATION HOLDER**
Bio-Health Limited
Culpeper Close
Medway City Estate
Rochester
Kent
ME2 4HU

8 **MARKETING AUTHORISATION NUMBER(S)**
THR 15817/0009

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
13/12/2011

10 **DATE OF REVISION OF THE TEXT**
13/12/2011
6 How to store this product

Do not use the capsules after the expiry date. The expiry data is printed on the bottle labels. The expiry data refers to the last day of that month. Return any unused capsules to your pharmacist who will dispose of them for you.

Store below 25°C in the original package.

Keep all medicines out of reach and sight of children.

Manufacturer and Traditional Herbal Registration Holder:

Bio-Health Ltd.
Culpin House
Medway City Estate
Rochester
Kent ME2 4HU.

Traditional Herbal Registration number:
THI 15817/0009

ID No: SIL 601

6 Further information

Each hard capsule of Silamarie contains the following active herbal ingredient:

Milk Thistle fruits 450mg (Silybum marianum L. Gaertner).

There are no other ingredients in Silamarie.

The capsule shell is made from hypromellose. The capsules are hard, clear, strong and contain a speckled brown powder.

Each bottle of Silamarie contains either 60 or 120 capsules.

For large prints, Braille or audio version please contact +44 (0) 1634 239110.
This leaflet was produced in December 2011.

*You can help to make medicines safer by reporting any side effects to the Yellow Card Scheme at www.mhra.gov.uk/yellcard. Alternatively you can get a paper reply card from your GP's surgery or pharmacy, or call free phone: 0800 030 8332 (Mon - Fri 9am - 5pm Monday - Friday).*

User Information Leaflet

MILK THISTLE FRUITS 450mg

Please read this leaflet carefully before using Silamarie. It contains important information about this medicine.

Keep this leaflet.
You may want to read it again. If you need more information or advice, please ask your doctor, pharmacist or qualified healthcare practitioner.

What is in this leaflet
1 What Silamarie is and what it is used for Page 2
2 Before you take Silamarie Page 2
3 How to take Silamarie Page 3
4 Side effects Page 4
5 How to store this product Page 5
6 Further information Page 6
1 What is Silamari and what it is used for
Silamari is a traditional herbal medicinal product, used to relieve symptoms associated with occasional over indulgence of food and drink, such as indigestion and upset stomach, based on traditional use only.

2 Before you take Silamari
Do not take if you:
- are allergic to any of the ingredients or to plants of the Asteraceae/Compositae family such as daisies, margarids or artichokes (see section 6).
- are pregnant or breastfeeding.
- are under 18 years of age.

Tell your doctor before taking this product if you are currently suffering from active liver disease.

3 How to take Silamari

Dosage
Swallow the capsules whole with water. Do not chew the capsules.

Adults and elderly:
To relieve the symptoms associated with occasional over indulgence of food and drink, such as indigestion and upset stomach.
Take 1 or 2 capsules 3 times daily swallowed with water up to a maximum of 6 capsules daily.

Do not exceed the recommended dose.
This product is not suitable for children or adolescents under 18 years of age.
If your symptoms worsen or persist for more than one week, consult your doctor or qualified healthcare practitioner.

If you take too much Silamari (overdose)
If you take more than the recommended dose, see a doctor, pharmacist or qualified healthcare practitioner and take this leaflet with you.

If you forget to take Silamari
Continue to take your usual dose at the usual time; it does not matter if you have missed a dose.

If you are unsure about anything relating to Silamari
If you have any questions, or are unsure about anything, please ask your doctor, pharmacist or qualified healthcare practitioner.

4 Side effects
Like all medicines this product may have side effects.

The following effects have been reported: nausea (feeling sick), upset stomach, diarrhoea and headache.

If these persist for more than a few days or become more troublesome, stop taking the product. The side effects are usually only temporary.

Other side effects include allergic reactions such as itching and/or skin rash, urticaria, hives, pruritis and anaphylaxis. If you experience an allergic skin reaction, stop taking the product and consult your doctor.

If you notice any other side effects after taking Silamari, please inform your doctor or pharmacist.

Continued...
LABELLING

Labels:

MILK THISTLE FRUITS 450mg
60 CAPSULES
Traditional herbal medicinal product
used to relieve symptoms associated
with occasional over indulgence of food
and drink, such as indigestion and upset
stomach, based on traditional use only.

Do not exceed the stated dose.
Keep out of reach and sight of children.
Store below 25°C in the original package.

If symptoms persist, or adverse reactions
occur, consult a doctor or qualified
healthcare practitioner.

RACH HARD CAPSUL CONTAINS
Milk Thistle fruits 450mg
(Silybum marianum L. Gaertn)

Silamarie is a traditional herbal medicinal
product used to relieve the symptoms
associated with occasional over indulgence
of food and drink, such as indigestion and upset
stomach, based on traditional use only.

Patients with known hypersensitivity to
Milk Thistle fruits should not use Silamarie.

If symptoms persist, or adverse reactions
occur, consult a doctor or qualified
healthcare practitioner.
Cartons: