PHYTOVEIN

THR 12297/0015

UKPAR

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The Medicines and Healthcare products Regulatory Agency (MHRA) granted LABORATOIRES ARKOPHARMA a Traditional Herbal Registration Certificate for the traditional herbal medicinal product PHYTOVEIN (Traditional Herbal Registration number: THR 12297/0015) on 24 May 2011. PHYTOVEIN is available without prescription and can be bought from pharmacies and other outlets.

PHYTOVEIN is a traditional herbal medicinal product used to relieve symptoms of discomfort and heaviness of the legs related to minor venous circulatory disturbances and to relieve symptoms of itching and burning associated with haemorrhoids, based on traditional use only. The active ingredient of PHYTOVEIN comes from Butcher’s broom (*Ruscus aculeatus* L.) rhizome.

This registration is based exclusively upon the longstanding use of Butcher’s broom rhizome 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.
PHYTOVEIN

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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 PHYTOVEIN (THR 12297/0015) to LABORATOIRES ARKOPHARMA on 24 May 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 symptoms of discomfort and heaviness of the legs related to minor venous circulatory disturbances and to relieve symptoms of itching and burning associated with haemorrhoids, based on traditional use only.

The data supplied by the applicant demonstrate 30 years of traditional use of Butcher’s broom rhizome, including at least 15 years of use in the European Community. A satisfactory review of the available safety data on Butcher’s broom rhizome has also been provided, together with an Expert Safety Report supporting the proposed product.
**PHARMACEUTICAL ASSESSMENT**

**HERBAL SUBSTANCE:**

<table>
<thead>
<tr>
<th>Latin name of the plant:</th>
<th>BUTCHER’S BROOM RHIZOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common name of the plant:</td>
<td><em>Ruscus aculeatus</em> L.</td>
</tr>
<tr>
<td>Family:</td>
<td>Butcher’s broom (En.), petit houx (Fr.), stechender Mäusedorn (Ger.)</td>
</tr>
<tr>
<td>Parts of the plant used:</td>
<td>Liliaceae</td>
</tr>
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<td></td>
<td>Rhizome</td>
</tr>
</tbody>
</table>

**Manufacture**

The herbal substance is collected manually from the wild in Macedonia in accordance with Good Agricultural and Collection Practice (GACP) guidelines. Collection takes place between March and April. Following collection the herbal substance is dried naturally in the shade and open air, protected from sunlight. As this herbal substance is collected from the wild, no pre-collection chemical treatments are applied. Assurance has also been provided that no chemical treatments are applied after collection. The herbal drug is stored in a dark warehouse that is refrigerated and humidity controlled.

Although there are concerns about the sustainability of Butcher’s broom in some countries, these issues do not currently appear to affect Macedonia. The applicant has confirmed that they will keep abreast of any sustainability issues and respond to any developments.

**Control of Herbal Substance**

An appropriate specification based on the Ph Eur monograph is applied and is acceptable. The specification is supported by the batch data provided.

**Reference Standards or Materials**

Suitable Certificates of Analysis have been provided for the reference substances used.

**Container Closure System**

The herbal substance is stored in an appropriate container. All components of the container closure system comply with Directive 2008/39/EC relating to plastic materials and articles intended to come into contact with foodstuffs.

**Stability**

Stability testing has been carried out on batches. The stored samples were tested in accordance with the proposed specification and the results show that at all time points the samples were within specification, supporting a suitable retest period.

**HERBAL PREPARATION: POWDERED BUTCHER’S BROOM RHIZOME**

The herbal preparation consists simply of the powdered herbal substance; this is produced prior to filling into the capsules as part of the herbal product manufacturing process. The herbal preparation is not stored.
**HERBAL PRODUCT:** PHYTOVEIN

**Description and Composition of the Herbal Product**
PHYTOVEIN are clear, hard capsules. The hypromellose capsule shells are filled with the herbal preparation (powdered Butcher’s broom) and the excipients colloidal hydrated silica and magnesium stearate.

The choice of excipients is based on experience and compatibility of the chosen excipients with the herbal substance is confirmed by stability testing. The colloidal hydrated silica and magnesium stearate comply with their respective Ph Eur monograph. The hypromellose complies with an appropriate in-house specification. Representative Certificates of Analysis has been provided for each excipient and are satisfactory.

The magnesium stearate used in the product is confirmed to be of vegetable origin and, therefore, carries no TSE risk.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided. The manufacturing method is a standard procedure.

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.

**Reference Standards or Materials**
Suitable details have been provided for the reference standards used.

**Container Closure System**
The product is stored in brown polyvinyl chloride bottles of 45 capsules, with a security cap made of low density polyethylene. Specifications and certificates are provided from the manufacturers of all container components. Confirmation is provided that all components of the container closure system comply with Directive 2008/39/EC relating to plastic materials and articles intended to come into contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a product shelf-life of 3 years is appropriate when the storage precautions ‘Do not store above 30°C’ and ‘Keep the bottle tightly closed’ are applied.
Assessor’s comments on the Summary of Product Characteristics, label and Patient Information Leaflet
All product literature is satisfactory.

A package leaflet has been submitted to the MHRA together 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.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY
The grant of a Traditional Herbal Registration is acceptable.
NON-CLINICAL ASSESSMENT

NONCLINICAL ASPECTS
The Expert Safety Report submitted by the applicant lists relevant references to published work studying the toxicology of Butcher’s broom rhizome.

NONCLINICAL OVERVIEW
The applicant has submitted a literature review with this application. An Expert Safety Report was provided, which included reviews of some non-clinical data. The Expert Safety Report was written by a pharmacist with suitable expertise.

The overview submitted in support of this application is satisfactory.

Due to a shortage of published data on Butcher’s broom rhizome, it is not possible to assess if the safety package for the phytochemical constituents of Butcher’s broom rhizome 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 is acceptable and in compliance with guideline EMEA/HMPC/32116/05.

Assurance was provided that the results of genotoxicity testing will be provided before renewal of the registration.

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
The information supplied demonstrates the traditional use of Butcher’s broom rhizome. An adequate literature review of Butcher’s broom rhizome has been carried out by the applicant and no new non-clinical data was submitted for assessment with this application. Granting of a THR is acceptable.
CLINICAL ASSESSMENT

PROPOSED INDICATION
The applicant has submitted the following therapeutic indication:

“Traditional herbal medicinal product used to relieve symptoms of discomfort and heaviness of the legs related to minor venous circulatory disturbances, based on traditional use only.
Traditional herbal medicinal product used to relieve symptoms of itching and burning associated with haemorrhoids, based on traditional use only.”

The indication is acceptable.

POSOLOGY AND METHOD OF ADMINISTRATION
The applicant has submitted the following:

“Oral use.

Adults and the elderly:
1 capsule, 3 times daily during meals, with a large glass of water.

Children and adolescents
The use in children or adolescents under 18 years of age is not recommended (See Section 4.4. ‘Special warnings and precautions for use.’)

Duration of use
If the symptoms persist for more than 2 weeks during the use of the medicinal product, a doctor or a qualified healthcare practitioner should be consulted.”

This is acceptable.

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

EVIDENCE OF LONG-STANDING 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 report describing the traditional use of Butcher’s broom rhizome within the EU for a period exceeding 30 years. Also, the Committee on Herbal Medicinal Products (HMPC) have adopted a monograph for Butcher’s broom rhizome that adequately covers the evidence for traditional use of the extract in the product under assessment in the EU for at least 30 years. The requirements of the Directive are, therefore, addressed for this aspect.
SAFETY REVIEW
Article 16 c 1 (D) requires the applicant to provide a bibliographic review of safety data, together with an expert report.

The HMPC assessment report for Butcher’s broom rhizome covers the bibliographic data available and the safety of Butcher’s broom rhizome has been demonstrated. The SmPC is in line with the HMPC monograph.

ASSESSMENT OF SUITABILITY FOR GSL STATUS
Butcher’s broom rhizome was assessed for suitability for GSL status. Section 51 of the Medicines Act 1968 states that “GSL may be appropriate for medicines which can, with reasonable safety, be sold or supplied otherwise than by or under the supervision of a pharmacist”. The term “reasonable safety” may usefully be defined as: “Where the hazard to health and the risk of misuse and the need for special precautions in handling are small, and where wider sale would be a convenience to the purchaser”.
1. Hazard to health
   There appears to be a minimal risk of hazard to health.
2. Risk of misuse
   In essence the risk of misuse of this product is felt to be low.
3. Need to take special precautions in handling
4. Wider sales are convenient to the purchaser
   It is considered that the four criteria for GSL status have been met and this product is suitable for GSL status.

PRODUCT LITERATURE
The product literature (Summary of Product Characteristics, Patient Information Leaflet and labelling) for this product are medically satisfactory.

DISCUSSION
The data supplied by the applicant demonstrate use for at least 30 years, of which at least 15 years have been in an EU Member State, as required for registration under the Traditional Herbal Medicines Product Directive. A satisfactory review of the available safety data relating to Butcher’s broom rhizome has been provided together with an expert report supporting the registration of the product.

RECOMMENDATIONS
A Traditional Registration may be granted.
OVERALL CONCLUSION AND RISK ASSESSMENT

QUALITY
The quality data submitted with this application are satisfactory.

NON-CLINICAL
No non-clinical data were submitted with this application. The results of genotoxicity testing will be provided before the THR is renewed. This is satisfactory.

EFFICACY AND SAFETY
No clinical efficacy data are required for registration of Traditional Herbal Medicinal Products.

The published HMPC assessment report and community monograph for Butcher’s broom rhizome adopted by the HMPC adequately covers the evidence for traditional use of the extract in the product under assessment for at least 30 years in the EU and the safety issues associated with Butcher’s broom rhizome.

The SmPC, PIL and labelling are satisfactory.

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

THR 12297/0015

STEPS TAKEN FOR ASSESSMENT

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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Traditional Herbal Registration application on 11 January 2010</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 18 January 2010</td>
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<tr>
<td>3</td>
<td>Pharmaceutical, preclinical and clinical issues were raised in relation to this application at the Herbal Medicine Advisory Committee (HMAC) meeting on 17 March 2010</td>
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<tr>
<td>4</td>
<td>The applicant addressed the issues raised by the HMAC on 27 September 2010</td>
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<tr>
<td>5</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 8 November 2010</td>
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<tr>
<td>6</td>
<td>The applicant responded to the MHRA’s request, providing further information on the quality dossier on 23 May 2011</td>
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<tr>
<td>7</td>
<td>A THR was granted on 24 May 2011</td>
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</table>
1 NAME OF THE MEDICINAL PRODUCT
PHYTOVEIN

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 350 mg of Butcher’s Broom rhizome (Ruscus aculeatus L., rhizome)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule, hard
Clear, size 0 hard capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Traditional herbal medicinal product used to relieve symptoms of discomfort and heaviness of the legs related to minor venous circulatory disturbances, based on traditional use only.
Traditional herbal medicinal product used to relieve symptoms of itching and burning associated with haemorrhoids, based on traditional use only.

4.2 Posology and method of administration
Oral use.

Adults and the elderly:
1 capsule, 3 times daily during meals, with a large glass of water.

Children and adolescents
The use in children or adolescents under 18 years of age is not recommended
(See Section 4.4. ‘Special warnings and precautions for use.’)

Duration of use
If the symptoms persist for more than 2 weeks during the use of the medicinal product, a doctor or a qualified healthcare practitioner should be consulted.

4.3 Contraindications
Hypersensitivity to the active substance or any of the excipients

4.4 Special warnings and precautions for use
Do not exceed the stated dose
There is no relevant use in children and adolescents under 18 years of age.
If there is inflammation of the skin or subcutaneous induration, ulcers, sudden swelling of one or both legs, cardiac or renal insufficiency, a doctor should be consulted. If diarrhoea develops, treatment should be discontinued. If rectal bleeding occurs a doctor should be consulted.

4.5 Interaction with other medicinal products and other forms of interaction
None reported.

4.6 Pregnancy and lactation
Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

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
Nausea, gastrointestinal complaints, diarrhoea, lymphocytic colitis may occur. 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. Symptomatic and supportive measure should be taken 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
Tests on carcinogenicity and reproductive toxicity have not been performed. Adequate tests on genotoxicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Colloidal hydrated silica
Magnesium stearate
Hypromellose (capsule shell).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 30°C. Keep the bottle tightly closed.

6.5 Nature and contents of container
Brown polyvinyl chloride bottle of 45 capsules, with a security cap made of low density polyethylene.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
LABORATOIRES ARKOPHARMA
Lid de Carros Le Broc-1er avenue, 2709 m
06510 CARROS
FRANCE
Tél.: +33 (0)4 93 29 11 28
Fax.:+33 (0)4 93 29 11 62

Trading as :
ARKOPHARMA
LABORATOIRES PHARMACEUTIQUES
Lid de Carros Le Broc-1er avenue, 2709 m
06510 CARROS
FRANCE

8 MARKETING AUTHORISATION NUMBER(S)
THR 12297/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/05/2011

10 DATE OF REVISION OF THE TEXT
24/05/2011
6 - FURTHER INFORMATION

What PHYTOVEIN contains
- Each hard capsule contains 350 mg of Butcher’s broom rhizome (Ruscus aculeatus L., rhizome).
- The other ingredients are magnesium stearate, colloidal hydrated silica and hypromellose (capsule shell).

What PHYTOVEIN looks like and contents of the pack
Each pack contains 45 capsules
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.

Traditional Herbal Registration Holder and Manufacturer
LABORATOIRES ARKOPHARMA
LID de Carros Le Broc – 1er avenue, 2709 m
06510 CARROS - France
Tel.: (+33) (0) 4 93 29 11 28 - Fax: (+33) (0) 4 93 29 11 62

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World Foods
Unit 7 Decade Close
High Carr Business Park
Newcastle under Lyme
ST5 7UH - Tel: +44 (0) 1782 564512

This leaflet was last approved in May 2011
Traditional Herbal Registration Number
THR 12297/0015

For a large print, call +44 (0)1782 564512 or email to enquiries@wfbm.co.uk

PHYTOVEIN, capsules
Butcher's broom rhizome 350 mg

Read all of this leaflet carefully before you start taking this medicine.
It contains important information for your treatment.

This medicine is available without prescription. However, you still need to take
PHYTOVEIN carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Ask your doctor or qualified healthcare practitioner if you need more
  information or advice.
- You must contact a doctor or qualified healthcare practitioner if your
  symptoms worsen or do not improve after 2 weeks.
- 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.

IN THIS LEAFLET:
1. What PHYTOVEIN is and what it is used for
2. Before you take PHYTOVEIN
3. How to take PHYTOVEIN
4. Possible side effects
5. How to store PHYTOVEIN
6. Further information

1 - WHAT PHYTOVEIN IS AND WHAT IT IS USED FOR

PHYTOVEIN is a traditional herbal medicinal product used
- to help relieve the symptoms of discomfort and tired heavy legs
  associated with varicose veins.
- to reduce itching & burning associated with haemorrhoids

This is based on traditional use only.
2 - BEFORE YOU TAKE PHYTOVEIN

DO NOT TAKE PHYTOVEIN IF
- you are allergic (hypersensitive) to the active substance or to any of the other ingredients (see Section 6 Further Information).
- you have been told by your doctor that you have heart or kidney failure.
- you are under 18 years old.

TAKE SPECIAL CARE WITH PHYTOVEIN
- Do not take more than the stated dose.
- Varicose leg ulcers can arise on your lower legs as a result of varicose veins. If you suffer from leg ulcers or if they develop, you must see your doctor before starting or continuing to use this product.
- Tell your doctor or a qualified healthcare practitioner if:
  - you notice inflammation of the skin or abnormally hard areas, sudden swelling of one or both legs;
  - rectal bleeding occurs;
  - side effects not mentioned in this leaflet occur;
  - your symptoms worsen or persist after 2 weeks;
- If diarrhoea develops, you should discontinue your treatment and consult your doctor.

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

PREGNANCY & BREAST FEEDING:
Do not use if you are pregnant or breast-feeding.

DRIVING AND USING MACHINES
No studies have been performed. However it is unlikely to affect your ability to drive or use machines.

3 - HOW TO TAKE PHYTOVEIN

Adults and the elderly: Take 1 capsule, 3 times daily during meals, with a large glass of water.

If your symptoms worsen or do not improve after 2 weeks during the use of PHYTOVEIN, consult your doctor or a qualified healthcare care practitioner.

Not for use in children or those under 18 years. For oral use only.

Don’t take more than the stated dose.

IF YOU TAKE MORE PHYTOVEIN THAN YOU SHOULD
If you take too much and feel ill, talk to your doctor.

IF YOU FORGET TO TAKE PHYTOVEIN
Do not take a double dose to make up for a forgotten dose.

IF YOU STOP TAKING PHYTOVEIN
You can stop taking PHYTOVEIN at any time.

4 - POSSIBLE SIDE EFFECTS

Like all medicines, PHYTOVEIN can have side effects, although not everybody gets them.

Nausea, gastrointestinal complaints, diarrhoea, lymphocytic colitis (non-bloody, watery diarrhoea) may occur.

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.

You can help to make medicines safer by reporting any side effects to the Yellow Card Scheme at www.yellowcard.gov.uk.
Alternatively you can get a paper Yellow Card form from your GP’s surgery or pharmacy, or call free phone 0808 100 3352 (available 10am-2pm Monday-Friday).

5 - HOW TO STORE PHYTOVEIN

Keep out of the reach and sight of children.

Do not use PHYTOVEIN after the expiry date which is stated on the bottle after “Exp”. The expiry date refers to the last day of that month.

Store in the original package and keep bottle tightly closed. Store below 30°C.
LABELLING
Label:

PHYTOVEIN Capsules
Butcher's broom rhizome 350 mg

DOSSAGE: for oral use.
Traditional herbal medicinal product used to relieve symptoms of:
- discomfort and tired heavy legs associated with varicose veins,
- itching and burning associated with haemorrhoids,
based on traditional use only.

DIRECTIONS FOR USE:
For oral use only. Read leaflet carefully before use.
Adults and the elderly: take 1 capsule, 3 times daily during meals, with a large glass of water.
If your symptoms persist or do not improve after 2 weeks during the use of PHYTOVEIN, a doctor or qualified health care practitioner should be consulted.

ACTIVE INGREDIENTS:
One hard capsule contains 350 mg of Butcher's broom, rhizome (Ruscus aculeatus L., rhizome).

THR 12297/0015
EXPIRY DATE: SEE ON THE SIDE
45 CAPSULES, hard

Distributed in UK by:

World Foods
Unit 7 Codden Crome
High Cumar Business Park
Mansfield Woodhouse
ST5 8KK • Tel: +44 (0) 1773 564512