

# **Phynova Joint and Muscle Relief Tablets**

**THR 41783/0001**

**UKPAR**

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# PHYNOVA JOINT AND MUSCLE RELIEF TABLETS

THR 41783/0001

## LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Phynova Group Ltd a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Phynova Joint and Muscle Relief Tablets (Traditional Herbal Registration number: THR 41783/0001) on 18th February 2015. Phynova Joint and Muscle Relief Tablets are available without prescription and can be bought from pharmacies and other outlets.

The active ingredient in Phynova Joint and Muscle Relief Tablets comes from the aerial parts of the *Sigesbeckia orientalis* L. subsp. *pubescens* (Makino) H. Koyama plant\*. Phynova Joint and Muscle Relief Tablets is a traditional herbal medicinal product used for the relief of backache, minor sports injuries, rheumatic or muscular pains and general aches and pains in the muscle and joints, based on traditional use only.

This registration is based exclusively upon the longstanding use of *Sigesbeckia orientalis* L. subsp. *pubescens* aerial parts 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.

\**Sigesbeckia pubescens* is used in the scientific literature. However the correct botanical name is as above.

# PHYNOVA JOINT AND MUSCLE RELIEF TABLETS

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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 Phynova Joint and Muscle Relief Tablets (THR 41783/0001) to Phynova Group Ltd on 18th February 2015. 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. Phynova Joint and Muscle Relief Tablets is a traditional herbal medicinal product used for the relief of backache, minor sports injuries, rheumatic or muscular pains and general aches and pains in the muscle and joints, based on traditional use only.

There is sufficient evidence to demonstrate use of *Sigesbeckia orientalis* L. subsp. *pubescens* aerial parts for at least 30 years, of which at least 15 years have been in an EU Member State. A satisfactory review of the available safety data on *Sigesbeckia orientalis* L. subsp. *pubescens* aerial parts has also been provided, together with an Expert Safety Report supporting the proposed product.

## **PHARMACEUTICAL ASSESSMENT**

**HERBAL SUBSTANCE:** *SIGESBECKIA ORIENTALIS* L. SUBSP.  
*PUBESCENS* AERIAL PARTS

**Scientific name of the plant:** *Sigesbeckia orientalis* L. subsp. *pubescens*  
(Makino) H. Koyama  
**Common names:** St Paul's wort (English)  
Xi Xiao Cao (Chinese)  
**Plant family:** Compositae

### **Manufacture of Herbal Substance**

The plants are collected from the wild in China. The whole aerial parts are collected before flowering or during the flowering season in the summer or early autumn. Following collection, the plants are washed, softened slightly, cut into sections and dried.

The plants are collected in accordance with the principles of Good Agricultural and Collection Practice (GACP) guidelines. It is also stated that the plants are not treated with pesticides, herbicides, fungicides or ethylene oxide.

### **Control of Herbal Substance**

An appropriate specification is applied taking account of current guidelines and pharmacopoeial requirements and is acceptable. The specification is supported by the batch data provided.

### **Container Closure System**

Satisfactory details of the container closure system are provided and confirmation has been given that all components of the container closure system comply with current legislation relating to plastic materials and articles intended to come into contact with foodstuffs.

### **Stability of Herbal Substance**

Confirmation is given that the herbal substance will be tested immediately prior to being used to make the herbal preparation. A shelf-life for the herbal substance is not necessary because it is only a precursor of the active substance, the herbal preparation. The actual guideline requires stability testing data for the herbal preparation and the herbal product in the application documents and not for the herbal substance.

**HERBAL PREPARATION:** *SIGESBECKIA ORIENTALIS* L. SUBSP.  
*PUBESCENS* DRY AERIAL PARTS  
AQUEOUS EXTRACT

**Extraction solvent:** Water  
**Drug extract ratio (native):** 8-10:1

### **Manufacture of Herbal Preparation**

A satisfactory description of the manufacturing process of the herbal preparation and

flow diagram has been provided. The in-process controls are satisfactorily detailed. Certificates of Analysis for all materials used in the manufacture of the herbal preparation have been provided.

#### **Control of Herbal Preparation**

A satisfactory specification with appropriate tests and limits has been provided for the herbal preparation.

Satisfactory analytical procedures are used to control the quality of the herbal preparation. Analytical procedures have been validated, as appropriate.

Certificates of Analysis have been provided for batches of the herbal preparation, demonstrating satisfactory compliance with the proposed specifications.

#### **Container Closure System**

Satisfactory details of the container closure system are provided and confirmation has been given that all components of the container closure system comply with current legislation relating to plastic materials and articles intended to come into contact with foodstuffs.

#### **Stability of Herbal Preparation**

Stability studies have been carried out under ICH conditions. The results support the proposed retest period of the herbal preparation.

### **HERBAL PRODUCT: PHYNOVA JOINT AND MUSCLE RELIEF TABLETS**

#### **Description and Composition of Herbal Product**

Phynova Joint and Muscle Relief Tablets are pale yellow, oval shaped, biconvex and film coated. Each tablet contains 500 mg aqueous extract from the dry aerial parts of the *Sigesbeckia orientalis* L. subsp. *pubescens* plant and the excipients dicalcium phosphate, microcrystalline cellulose, magnesium stearate, silicon dioxide, croscarmellose sodium, stearic acid, hydroxypropyl methylcellulose, titanium dioxide, purified talc and mastercote yellow.

The compatibility of the herbal preparation with the excipients is demonstrated by the stability testing results. The excipients are controlled in line with their respective Ph Eur monographs with the exception of silicon dioxide, which is controlled in line with the USNF, and mastercote yellow, which is controlled by a suitable in-house specification. In the absence of Ph Eur monographs for these excipients this is acceptable.

Satisfactory Certificates of Analysis are provided for all excipients.

None of the excipients are derived from animal material.

#### **Manufacture of Herbal Product**

A satisfactory batch formula has been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. The

manufacturing process has been validated with pilot scale batches and a validation protocol reflecting the full scale batch is provided and is satisfactory.

### **Control of Herbal Product**

The finished product specifications are 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 tablets are stored in either blister packs composed of 250µm PVDC (white opaque) with aluminium foil (20µm) or snap secure polypropylene pots with HDPE caps (58x49mm). The blisters packs contain 15 tablets per pack with 2, 4 or 6 packs in each carton. The pots contain 60 tablets.

Suitable specifications have been provided by the packaging suppliers and it has been confirmed that all primary packaging materials comply with EU Directive and food regulations.

### **Stability of Herbal Product**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a product shelf-life of 24 months is appropriate when the storage precaution 'This medicinal product should not be stored above 25°C' is applied.

### **Pharmaceutical Expert**

The Quality Overall Summary has been written by an expert with suitable sufficient pharmaceutical and pharmacognosy experience.

### **Product Literature**

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**

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 suitably qualified professional.

The overview submitted in support of this application is satisfactory.

Due to a shortage of published data on *Sigesbeckia orientalis* L. subsp. *pubescens* (Makino) H. Koyama aerial parts it is not possible to assess if the safety package for the phytochemical constituents of this active ingredient 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.

In an Ames assay, *Sigesbeckia* dry extract was not mutagenic.

### **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.



## **CLINICAL ASSESSMENT**

### **INDICATIONS**

The applicant submitted the following therapeutic indications:

“A traditional herbal medicinal product used for the relief of backache, minor sports injuries, rheumatic or muscular pains and general aches and pains in the muscle and joints, based on traditional use only”

These indications are acceptable.

### **POSOLOGY AND METHOD OF ADMINISTRATION**

The applicant has submitted the following:

“For oral administration

*Adults and elderly*: Take one tablet, twice daily (one in the morning and one at night).

Tablets should be swallowed whole with a little water or other liquid.

This product is not recommended for use in children and adolescents under 18 years of age (See ‘section 4.4 special warnings and precautions for use’).

If symptoms worsen, or do not improve after 4 weeks, a doctor or a qualified healthcare practitioner should be consulted.”

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 showing 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.

There is sufficient evidence to demonstrate use of *Sigesbeckia orientalis* L. subsp. *pubescens* aerial parts 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 bibliographic review 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.

## **ASSESSMENT OF SUITABILITY FOR GSL STATUS**

*Sigesbeckia orientalis* L. subsp. *pubescens* aerial parts 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”.

### **Suitability of indication for GSL:**

#### 1. Hazard to health

There appears to be a minimal risk of hazard to health.

#### 2. Risk of misuse

The indications are clear and easily understandable to the patient. Doses are also clearly stated. Moreover other GSL products are available for the proposed indication. The risk of misuse of this product is considered to be low.

#### 3. Need to take special precautions in handling

There are no special precautions in handling this product other than keeping it out of the reach and sight of children (as with any other GSL medicine).

#### 4. Wider sales are convenient to the purchaser

This would apply.

In summary, it is considered that the four above criteria for GSL status have been met and this product should be suitable for GSL status.

## **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 RISK ASSESSMENT**

### **QUALITY**

The quality data submitted with this application are satisfactory.

### **NON-CLINICAL**

No new non-clinical data were submitted with this application. In an Ames assay, *Sigesbeckia* dry extract was not mutagenic.

### **EFFICACY AND SAFETY**

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

There is sufficient evidence to demonstrate use of *Sigesbeckia orientalis* L. subsp. *pubescens* aerial parts for at least 30 years, of which at least 15 years have been in an EU Member State, and a satisfactory review of the safety data has 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 risk: benefit balance is acceptable and a Traditional Herbal Registration may be granted.

## PHYNOVA JOINT AND MUSCLE RELIEF TABLETS

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### STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the Traditional Herbal Registration application on 28 November 2012.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 6 December 2012.
3	Following assessment of the response the MHRA requested further information relating to the clinical dossier on 11 February 2013.
4	The applicant responded to the MHRA's request, providing further information on the clinical dossier on 21 June 2013.
5	Following assessment of the response and a meeting of the Herbal Medicines Advisory Committee (HMAC) on 1 July 2013, the MHRA requested further information relating to the quality, non-clinical and clinical dossiers on 19 July 2013
6	The applicant responded to the MHRA's requests, providing further information on the quality, non-clinical and clinical dossiers on 1 April 2014
7	Following assessment of the response and a meeting of the HMAC on 23 July 2014, the MHRA requested further information relating to the quality, non-clinical and clinical dossiers on 28 July 2014
8	The applicant responded to the MHRA's requests, providing further information on the quality, non-clinical and clinical dossiers on 26 November 2014
9	A THR was granted on 18 February 2015

## **SUMMARY OF PRODUCT CHARACTERISTICS**

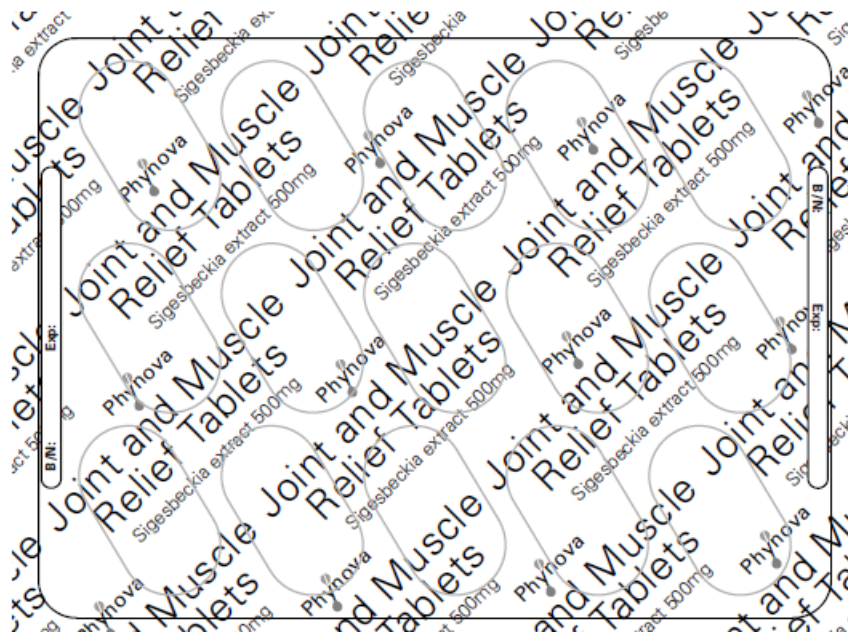
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website

## **PATIENT INFORMATION LEAFLET**

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

## LABELLING

### Blister:



### Label:

<p><b>Warning: Do not exceed the stated dose. Do not use if you are:</b></p> <ul style="list-style-type: none"> <li>• Allergic to <i>Sigesbeckia</i>, any plants of the Asteraceae (Compositae) family, or any of the ingredients.</li> <li>• Pregnant, trying to become pregnant or breast-feeding</li> <li>• Under 18.</li> </ul> <p><b>Keep out of the sight and reach of children.</b> Store in the original packaging. Do not store above 25°C. Do not use after the expiry date shown on the base of the carton.</p> <p><b>Manufactured in the UK</b> THR holder: Phynova Group Ltd, 16 Blenheim Office Park, Long Hanborough, OX29 8LN, UK. Tel: +44 (0) 1993 880 700</p>	<p>Phynova</p> <h3 style="margin: 0;">Joint and Muscle Relief Tablets</h3> <p>Sigesbeckia extract 500mg</p> <p>A traditional herbal medicinal product used for the relief of:</p> <ul style="list-style-type: none"> <li style="margin-right: 10px;">• backache</li> <li style="margin-right: 10px;">• minor sports injuries</li> <li style="margin-right: 10px;">• rheumatic or muscular pains</li> <li>• general aches and pains in the muscles and joints</li> </ul> <p>based on traditional use only</p>	<p><b>Active ingredient:</b> Each film coated tablet contains 500mg of extract (as dry extract) from <i>Sigesbeckia orientalis</i> L. subsp. <i>pubescens</i> aerial parts (equivalent to 4- 5g of <i>Sigesbeckia orientalis</i> L. subsp. <i>pubescens</i> (Makino) H. Koyama). Extraction solvent: water. Please read the enclosed leaflet before taking the tablets. For oral use only.</p> <p><b>Dosage: Adults &amp; the elderly:</b> Take one tablet twice daily (one in the morning and one at night). Tablets should be swallowed whole with a little water or other liquid. This product is not recommended for use in children and adolescents under 18 years of age. You must consult your doctor or qualified healthcare practitioner if:</p> <ul style="list-style-type: none"> <li>• your joint pain is accompanied by swelling of the joint, redness or fever</li> <li>• your symptoms worsen, or do not improve after 4 weeks.</li> </ul>
<p>THR 41783/0001</p>	<p>60 Tablets</p>	<p style="font-size: small;">Certification Mark </p>

**Cartons:**





