

Digestherb hard capsules

THR 23056/0005

UKPAR

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DIGESTHERB HARD CAPSULES

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Schwabe Pharma (UK) Ltd a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Digestherb hard capsules (Traditional Herbal Registration number: 23056/0005). This product is available without prescription and can be bought from pharmacies and other outlets.

Digestherb hard capsules are used for the relief of digestive complaints such as indigestion, upset stomach, nausea, feelings of fullness and flatulence (wind) particularly when caused by over indulgence of food and drink, based on traditional use only. The tablets' active ingredient is dry extract from the leaves of the artichoke plant, also known as *Cynara scolymus* L. This registration is based exclusively upon evidence of traditional use of artichoke leaf as a herbal medicine and not upon data generated from clinical trials. There is no requirement under the Traditional Herbal Registration scheme to prove scientifically that the 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 Digestherb hard capsules to Schwabe Pharma (UK) Ltd on 19 February 2009. This product is on the general sales list (GSL).

The application was submitted under Article 16.c of Directive 2001/83 EC, as amended, as part of the Traditional Herbal Medicines Registration Scheme.

This product consists of hard capsules containing 400 mg of dry extract from leaves of the artichoke plant (*Cynara scolymus* L.) The product is used for the relief of digestive complaints, such as indigestion, upset stomach, nausea, feelings of fullness and flatulence (wind), particularly caused by over indulgence of food and drink

This THR is based exclusively on evidence of traditional use of artichoke leaf. The recommended dose is one capsule twice daily.

The data supplied by the applicant demonstrate 30 years of traditional use of artichoke leaf in the European Community. A satisfactory review of the available safety data on artichoke leaf has also been provided, together with an expert safety report supporting the proposed product.

PHARMACEUTICAL ASSESSMENT

HERBAL SUBSTANCE: ARTICHOKE LEAVES

General information

Scientific name of the plant:	<i>Cynara scolymus L.</i>
Family:	Asteraceae (Compositae)
Parts of the plant used:	Dried, whole or cut basal leaves

Manufacture

The plant source of the herbal substance artichoke leaves is *Cynara scolymus L.* belonging to the Asteraceae (Compositae) family. It is indigenous to the whole of the Mediterranean region, the Canary Islands and South America. The plant is cultivated in Europe and North Africa.

The plant material used in Digestherb hard capsules is cultivated in Poland and Germany. The leaves are mechanically harvested before flowering, from July to October and dried before being stored protected from light.

The supplier of the artichoke leaves has provided confirmation that the herbal substance is cultivated under controlled conditions and that storage is in dry, well ventilated warehouses protected from pests.

During cultivation the crops are treated with fertiliser and herbicide but assurance has been provided from the supplier of the artichoke leaves that fungicides and fumigant treatments have not been used and the plant material has not been irradiated.

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.

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 Directive 2002/72/EC relating to plastic materials and articles intended to come into contact with foodstuffs.

Stability

Satisfactory stability data are provided that support the suggested retest period.

HERBAL PREPARATION: ARTICHOKE LEAVES DRY EXTRACT

General information

Herbal preparation:	Artichoke leaves dry extract
Scientific name of the plant:	<i>Cynara scolymus L.</i>
Parts of the plant used:	Dried whole or cut basal leaves
Ratio of the herbal substance to the herbal preparation (native):	4-6:1
Extraction solvent:	Water

The dry extract preparation is a brownish powder with a characteristic odour and a very bitter taste. It consists of native extract, lactose monohydrate and colloidal anhydrous silica.

Manufacture

Manufacture of the herbal preparation is a standard procedure. A satisfactory description of the manufacturing process and a flow diagram has been provided.

Certificates of analysis for all materials used in the manufacture of the herbal preparation are provided. All excipients are tested and released according to their Ph. Eur. monograph apart from water, which is controlled according to the manufacturer's monograph which was based on German drinking water regulations.

Satisfactory in-process controls are in place during manufacture to ensure the quality of the herbal preparation.

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 production batches of the herbal preparation, demonstrating satisfactory compliance with the proposed specification.

The proposed specification has been justified satisfactorily.

Container Closure System

The extract is stored in a suitable container. Specifications have been provided by the supplier together with the declaration of compliance with Directive 2002/72/EC.

Stability

Stability studies have been carried out on batches of the herbal preparation under ICH long term and accelerated conditions. The proposed retest period for the dry extract is 12 months when stored below 25°C protected from heat, light and moisture.

HERBAL PRODUCT

Description and Composition of the Herbal Product

The formulation is straightforward and combines the active ingredient with well known pharmaceutical excipients, namely, talc, magnesium stearate, colloidal anhydrous silica, maize starch, lactose monohydrate, gelatin, titanium dioxide E171, sodium lauryl sulfate, iron (III)-oxide E172 (red iron oxide), iron oxide hydrate E172 (yellow iron oxide) and chlorophyllin copper complex E141.

The choice of excipients is based on experience and compatibility of the chosen excipients with the drug substance, which is confirmed by stability testing. Interaction of the herbal product with the container is not expected based on the results of stability testing.

Control of Excipients

All the excipients and analytical procedures are as specified by the Ph Eur monographs. In addition, the hard gelatine capsules comply with the Ph Eur category 3A for microbial quality and the colouring agent, titanium dioxide E171, complies with Directive 95/45/EC. Water used in the manufacture of the finished product is purified water corresponding to the standards of the Ph Eur.

The applicant has confirmed that the magnesium stearate used to make the herbal product is of vegetable origin. Appropriate certification has been provided from the supplier confirming this. Confirmation has been provided that the lactose monohydrate is obtained from milk suitable for human consumption. Appropriate certification has been provided for the gelatine. All colouring

agents are listed in the European directive 94/36/EC comply with the requirements set in the directive.

Manufacture

The manufacturing method is a standard procedure and is satisfactory.

A number of in-process control tests are performed during the manufacturing process to ensure the quality of the product. All are considered adequate.

Control of Herbal Product

The finished product specifications at release and end of shelf life are detailed and the tests and limits used were found to be satisfactory for a product of this nature.

Satisfactory details have been provided on all analytical procedures and these analytical procedures are valid.

Certificates of Analysis have been presented for batches of the drug product demonstrating little inter-batch variation.

Reference Standards or Materials

Certificates of Analysis for all the markers, including the reference substance, have been provided by the finished product manufacturer.

Container Closure System

The product is presented in packs of 30, 60 or 90 capsules sealed into binary blisters made of PVC/PVDC and aluminium. Suitable specifications have been provided by the packaging suppliers. The components of the primary packaging system, including the sealing layer, comply with Directive 2002/72 relating to contact with foodstuffs.

Stability

Stability studies were conducted under ICH conditions on product batches in the container type proposed for marketing.

Based on the results, a proposed shelf life of 30 months with the storage condition "Do not store above 25°C" is justified.

PRODUCT LITERATURE

The product literature (Summary of Product Characteristics, Patient Information Leaflet and labelling) for this product are pharmaceutically 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.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY

This product is satisfactory and a Traditional Herbal Registration can be granted.

NON-CLINICAL ASSESSMENT

NONCLINICAL ASPECTS

The Expert Safety Report submitted by the applicant lists relevant references to published work studying the toxicology of artichoke leaves.

NONCLINICAL OVERVIEW

The applicant has submitted a literature review with this application. An Expert Report on Safety was provided, which included reviews of some non-clinical data.

The overview submitted in support of this application is satisfactory.

Due to a shortage of published data on artichoke leaves, it is not possible to assess if the safety package for the phytochemical constituents of artichoke leaves 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.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC for this product is satisfactory from a preclinical 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 demonstrating traditional use of artichoke leaves is acceptable. An adequate literature review of artichoke leaves 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

BACKGROUND INFORMATION

Artichoke products are currently widely available in the UK as herbal remedies exempt from licensing under Section 12(2) of the Medicines Act 1968. Artichoke leaf extract is used as an ingredient of one currently licensed product.

LEGAL STATUS

General Sales List (GSL) status is requested for the product. Artichoke is currently on the GSL order.

PROPOSED INDICATION

The applicant has proposed the following:

“Traditional herbal medicinal product used for the relief of digestive complaints, such as indigestion, upset stomach, , nausea, feelings of fullness and flatulence (wind), particularly caused by over indulgence of food and drink, based on traditional use only.”

The indication is acceptable. It is in agreement with the traditional uses of artichoke leaf. The proposed indication is considered acceptable for an over the counter (OTC) product and is in line with the wording currently permitted for Biostrath Artichoke Formula (PL 04210/0004; available OTC), which is used for symptomatic relief of indigestion after eating fatty foods. The product is considered suitable for use without the supervision of a medical practitioner.

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 Community.

The applicant has provided a bibliographic review which shows evidence for the use of *Cynara scolymus* within the EU for a period exceeding 30 years.

Assessor’s comment:

The information provided is considered to satisfactorily demonstrate that artichoke leaf extract has been in use for at least 30 years (of which at least 15 have been in an EU member state), and that its use covers the indications sought. The requirements of the directive are, therefore, satisfied.

SAFETY REVIEW

Article 16 c 1 (D) requires the applicant to provide a bibliographic review of safety data together with an expert report.

A safety review has been provided and an Expert Report written by a pharmacist with expertise in herbal medicines.

Assessor’s comment:

The safety review is acceptable and includes most major studies. Adverse events associated with this product appear to be generally mild.

PRODUCT LITERATURE

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

DISCUSSION

This is an application for registration under the Traditional Herbal Medicinal Products Directive. The data supplied by the applicant are sufficient to demonstrate 30 years of traditional use within the Community for corresponding products. An acceptable review of the available safety data on artichoke leaf has been provided together with an Expert Report supporting the proposed product.

RECOMMENDATIONS

A Traditional Registration may be granted.

OVERALL CONCLUSION AND RISK ASSESSMENT

QUALITY

The quality data submitted with this application are satisfactory.

PRECLINICAL

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

EFFICACY AND SAFETY

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

The Applicant has provided a bibliographic review which shows ample evidence for the use of artichoke leaves within the EU for a period exceeding 30 years.

A satisfactory review of the safety data has been provided.

The SPC, PIL and labelling are satisfactory.

RISK ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.

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STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Traditional Herbal Registration application on 4 May 2006
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 14 September 2006
- 3 Following assessment of the application the MHRA requested further information relating to the quality dossier on July 2006 and the clinical dossier on 16 May 2007. The applicant responded to the MHRA's requests, providing further information on the clinical dossier on 1 December 2008 and 18 February 2009.
- 4 A THR was granted on 20 February 2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Digestherb hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

400mg of extract (as dry extract) from Artichoke leaf (*Cynara scolymus* L.) (equivalent to 1600-2400 mg of dry herb).

Extraction solvent: Water.

Each capsule contains 85 mg lactose.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard gelatin capsule

Green, opaque.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Traditional herbal medicinal product used for the relief of digestive complaints, such as indigestion, upset stomach, , nausea, feelings of fullness and flatulence (wind), particularly caused by over indulgence of food and drink, based on traditional use only.

4.2 Posology and method of administration

For oral use only. The patient should be advised to consult a doctor if symptoms do not improve after 1 week.

For adults and the elderly, take one capsule twice daily. The capsules should be swallowed whole with a little liquid before food.

Not for use in children and adolescents under 18 years.

4.3 Contraindications

Hypersensitivity to Artichoke or any of the other ingredients in the product.

Patients with gall stones or with a history of obstructive gall bladder disease.

Not recommended for use in children or adolescents under 18 years of age, or in pregnancy, or in lactation (see section 4.6).

4.4 Special warnings and precautions for use

This product contains lactose:

1 capsule contains max. 85 mg lactose.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There are no published data available on drug interactions with extracts of artichoke leaf.

4.6 Pregnancy and lactation

The safety of the product during pregnancy and lactation has not been established, therefore it should be avoided during pregnancy or while breast-feeding.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Undesirable effects associated with the use of artichoke leaf extract are generally mild and self limiting. The following undesirable effects have been reported in clinical studies:

Nausea

Increased flatulence

Diarrhoea

Asthenia

4.9 Overdose

In the event of an overdose, patients are advised to contact a doctor, pharmacist or healthcare professional. A small overdose (up to 8 capsules) may not cause any symptoms. In the event of a large overdose (more than 8 capsules), advice should be sought from a doctor.

Management of an overdose should include appropriate symptomatic and supportive treatment as warranted by the clinical situation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

No pharmacodynamic studies have been undertaken with Digestherb, the pharmacodynamic properties are unknown.

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been conducted with Digestherb or its active constituents.

5.3 Preclinical safety data

The non-clinical toxicology data available are limited. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Extract excipients:

Lactose monohydrate

Silica, colloidal anhydrous

Other excipients:

Talc
Magnesium stearate
Silica, colloidal anhydrous
Maize starch
Lactose monohydrate
Gelatin
Titanium dioxide E171
Sodium lauryl sulfate
Iron (III)-oxide E172 (=red iron oxide)
Iron oxide hydrate E172 (=yellow iron oxide)
Chlorophyllin copper complex E141

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life is 30 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Original packages containing 30, 60 or 90 capsules

Digestherb capsules are packed in PVC/PVDC- aluminium blisters and inserted into a carton.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Schwabe Pharma (UK) Ltd
Alexander House
Mere Park
Dedmere Road
Marlow
Buckinghamshire
SL7 1PD

8 MARKETING AUTHORISATION NUMBER(S)

THR 23056/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/02/2009

10 DATE OF REVISION OF THE TEXT

19/02/2009

PATIENT INFORMATION LEAFLET

Patient Information Leaflet

DigestHerb[®] hard capsules

Artichoke Leaf extract 400mg

Please read this leaflet carefully before you start taking these capsules. It contains some important information about DigestHerb.

Keep this leaflet with the capsules.

You may want to read it again or show it to your doctor, pharmacist or healthcare practitioner.

What is in this leaflet

1: What this product is and what it is used for.....	page 1
2: Before you take this product	page 2
3: How to take this product	page 2
4: Side-effects	page 3
5: After taking this product	page 3
6: Product description	page 4

1: What this product is and what it is used for

This product is a traditional herbal medicinal product containing Artichoke leaf. Each hard capsule of this product contains 400mg of extract (as dry extract) from Artichoke leaf (*Cynara scolymus* L.)(4-6:1) (equivalent to 1600-2400mg of Artichoke leaf). Extraction solvent: Water.

DigestHerb is a traditional herbal medicinal product used for the relief of digestive complaints, such as indigestion, upset stomach, nausea, feelings of fullness and flatulence (wind); particularly caused by over-indulgence of food and drink, based on traditional use only.

2: Before you take this product

DO NOT TAKE this product if you:

- have a history of **obstructive gall bladder disease**
- have **gallstones**
- are **lactose-intolerant** (react badly to lactose or milk)
- are **pregnant** or **breast-feeding**
- are **allergic to any of ingredients** (see section 6)
- are **under 18 years of age**

3: How to take this product

Adults and the elderly

Take 1 capsule twice daily – The capsule should be swallowed whole with a little liquid before food.

Do not exceed the stated dose.

If you take too much of this product (overdose)

If you take more than the recommended dose, speak to a doctor, pharmacist or healthcare practitioner and take this leaflet with you. A small overdose (up to 8 capsules) may not cause any symptoms. In the event of a large overdose (more than 8 capsules), advice should be sought from a doctor.

If you forget to take this product

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

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

2

4: Side-effects

Like all medicines, this product can have side-effects.

Side-effects associated with the use of artichoke leaf extract are generally mild and often only temporary.

The following side-effects have been reported in clinical studies:

- **Nausea**
- **Increased flatulence**
- **Diarrhoea**
- **Asthenia** (muscle weakness)

Tell your doctor or pharmacist if you notice any other side-effect.

5: After taking this product

You must speak to a healthcare practitioner if your symptoms do not improve after one week, or if side-effects not mentioned in this leaflet occur.

Do not use your capsules after the expiry date.

Return any out-of-date capsules to your pharmacist who will dispose of them for you. The expiry date is printed on the box and the blister pack.

Store the capsules in a cool dry place.

Do not store the capsules in a place where the temperature goes above 25°C.

Keep the capsules out of the reach and sight of children.

Keep your capsules in the blister pack until it is time to take them.

6: Product description

Each hard capsule contains 400mg of extract (as dry extract) from Artichoke leaf (*Cynara scolymus* L.) (4-6:1) (equivalent to 1600-2400mg of Artichoke leaf). Extraction solvent: Water.

This product also contains the following ingredients:

Talc, magnesium stearate, silica colloidal anhydrous, maize starch, lactose monohydrate, gelatin, purified water, titanium dioxide (E171), sodium lauryl sulphate, iron oxide hydrate (E172) (red and yellow iron oxide), chlorophyllin copper complex (E141).

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product.

Each hard capsule contains 85 mg of lactose.

Each pack contains 30, 60 or 90 capsules.

Registration holder for this product

Schwabe Pharma (UK) Ltd
Alexander House, Mere Park, Dedmere Road
Marlow, Bucks SL7 1PD

Manufacturer of this product

Wiewelhove GmbH
Gildestrasse 39, 49477 Ibbenbüren, Germany

Traditional herbal registration number: THR 23056/0005

If you would like further information about this product, please contact:

Schwabe Pharma (UK) Ltd
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Telephone: 01628 401980 Email: info@schwabepharma.co.uk

This leaflet was prepared in February 2009

For a large print, Braille or audio version of this leaflet, call 01628 401980

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LABELLING

