DiaCough Cough Syrup

THR 33518/0004

UKPAR

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The Medicines and Healthcare products Regulatory Agency (MHRA) granted Diapharm Regulatory Services GmbH a Traditional Herbal Registration Certificate for the traditional herbal medicinal product DiaCough Cough Syrup (Traditional Herbal Registration number: THR 33518/0004) on 28 February 2011. This product is available without prescription and can be bought from pharmacies and other outlets.

DiaCough Cough Syrup is a traditional herbal medicinal product used to relieve chesty coughs associated with the common cold based on traditional use only. The active ingredient of DiaCough Cough Syrup comes from ivy (Hedera helix L.) leaf.

This registration is based exclusively upon the longstanding use of ivy leaf 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.
DIACOUGH COUGH SYRUP

THR 33518/0004

SCIENTIFIC DISCUSSION

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The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal medicine DiaCough Cough Syrup (THR 33518/0004) to Diapharm Regulatory Services GmbH on 28 February 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 chesty coughs associated with the common cold, based on traditional use only.

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

HERBAL SUBSTANCE: IVY LEAF

Scientific name of the plant: *Hedera helix* L.
Family: Araliaceae

The ivy plants used in this product are collected manually from the wild, mainly in Eastern Europe and mainly in spring and summer. The plant material is dried and then stored protected from light, humidity and pests.

The sustainability of this collection method is guaranteed, as only the young twines of the mother plant are collected. The stem and roots of the plants remain intact.

Confirmation has been provided that the herbal substance is produced in line with the Guideline on Good Agricultural and Collection Practice (GACP) EMEA/HMPC/246816/2005. Controls are in place to exclude the possibility of any adulteration of the herbal substance by other plant species.

**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 2008/39/EC relating to plastic materials and articles intended to come into contact with foodstuffs.

**Stability**
Confirmation is given that the herbal substance will be tested prior to being used to make the herbal preparation. A shelf-life for the herbal substance is not appropriate 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: IVY LEAF DRY EXTRACT

Parts of the plant used: Leaf
Ratio of the herbal substance to the herbal preparation (native): 5-7.5:1
Extraction solvent: Ethanol 30% w/w

MHRA PAR; DIACOUGH COUGH SYRUP, THR 33518/0004
A satisfactory description of the manufacturing process of the herbal preparation and flow diagram has been provided. The in-process controls are satisfactorily detailed. The manufacture of the herbal preparation is considered a standard procedure.

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

**Container Closure System**
Confirmation is provided that all components of the container closure system used to store this herbal preparation comply with Directive 2008/39/EC relating to plastic materials and articles intended to come into contact with foodstuffs.

**Stability**
Stability studies have been performed in accordance with current guidelines. The proposed re-test period for the ivy leaf dry extract is acceptable.

**HERBAL PRODUCT: DIACOUGH COUGH SYRUP**

**Description and Composition of the Herbal Product**
DiaCough Cough Syrup is a light brown, slightly cloudy syrup. A dose of 5 ml of the cough syrup contains 35 mg of extract (as dry extract) from ivy leaf and the excipients potassium sorbate, anhydrous citric acid, xanthan gum, cherry flavour, sorbitol liquid 70% (crystallising) and purified water.

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 monograph, with the exception of the cherry flavour, which is controlled to an in-house specification; in the absence of an appropriate Ph Eur monograph for this excipient this is acceptable.

**Manufacture**
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 syrup is stored in glass bottles containing either 100 ml or 200 ml of the herbal product. Suitable specifications have been provided by the packaging suppliers and it has been confirmed that all primary packaging materials comply with Directive 2008/39/EC.

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. After the bottle is first opened a shelf life of 3 months is applied.

Pharmaceutical Expert
The Quality Overall Summary has been written by a pharmacist with extensive experience with herbal products.

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 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
The grant of a Traditional Herbal Registration is acceptable.
NON-CLINICAL ASSESSMENT

NON-CLINICAL ASPECTS
The Expert Safety Report submitted by the applicant lists relevant references to published work studying the toxicology of ivy leaf.

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 ivy leaf, it is not possible to assess if the safety package for the phytochemical constituents of these active ingredients 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
There are no objections to granting of a Traditional Herbal Registration from a non-clinical point of view.
CLINICAL ASSESSMENT

PROPOSED INDICATION
The applicant has submitted the following therapeutic indication:

“Traditional herbal medicinal product used to relieve chesty coughs associated with the common cold based on traditional use only.”

The indication is acceptable.

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

“For oral use only.
Shake the bottle well before use.
Adults, the elderly, children aged 12 years and over: take 5 ml of oral liquid using the enclosed measuring cup 3 times daily.

The syrup should be taken in the morning, at midday and in the evening.

Duration of use
If symptoms worsen or persist after 7 days, a doctor or qualified healthcare practitioner should be consulted.

The product should not be used for more than 2 weeks.
The use in children under 12 years of age is not recommended (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 (THMP).

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 information which shows evidence for the medicinal use of ivy leaf for more than 30 years, including at least 15 years within the EU. Therefore, there is sufficient evidence of traditional use of the herbal preparation and a traditional herbal registration can be granted.
SAFETY REVIEW
Article 16 c 1 (d) requires the applicant to provide a bibliography of the safety data together with an expert report.
The safety review has been provided, as well as an expert report written by a professional with relevant expertise. A CV has been included.
The applicant has provided satisfactory information supporting the safety of ivy leaf.

ASSESSMENT OF SUITABILITY FOR GSL STATUS
The suitability of this product for GSL status was review during the assessment of this THR application.
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
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.

RECOMMENDATIONS
A Traditional Herbal Registration may be granted.
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. However, assurance was provided that the results of genotoxicity testing will be provided before renewal of this registration. This is satisfactory.

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

The Applicant has provided information which shows evidence for the use of ivy leaf for a period exceeding 30 years, including at least 15 years within the EU.

A satisfactory review of the safety data has been provided.

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.
DIACOUGH COUGH SYRUP

THR 33518/0004

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Traditional Herbal Registration application on 14 August 2009.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 19 August 2009.
3. Pharmaceutical, preclinical and clinical issues were raised in relation to this application at the Herbal Medicine Advisory Committee (HMAC) meeting on 19 November 2009.
4. The applicant addressed the issues raised by the HMAC on 10 June 2010.
5. Following assessment of the response the MHRA requested further information relating to the dossier on 27 July 2010.
6. The applicant responded to the MHRA’s request, providing further information on the dossier on 25 October 2010.
7. Following assessment of the response the MHRA requested further information relating to the dossier on 1 November 2010.
8. The applicant responded to the MHRA’s request, providing further information on the dossier on 6 February 2011.
9. Following assessment of the response the MHRA requested further information relating to the dossier on 16 February 2011.
10. The applicant responded to the MHRA’s request, providing further information on the dossier on 21 February 2011.
11. A THR was granted on 28 February 2011.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
DiaCough Cough Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
5 ml of oral liquid contains 35 mg of extract (as dry extract) from ivy leaf (Hedera helix L.) (5-7.5:1)
Extraction solvent: ethanol 30% w/w.
For a full list of excipients, see section 6.1.
Each 5 ml of liquid contains 1926 mg sorbitol.

3 PHARMACEUTICAL FORM
Syrup
Light brown, slightly cloudy syrup.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Traditional herbal medicinal product used to relieve chesty coughs associated with the common cold based on traditional use only.

4.2 Posology and method of administration
For oral use only.
Shake the bottle well before use.
Adults, the elderly, children aged 12 years and over: take 5 ml of oral liquid using the enclosed measuring cup 3 times daily.

The syrup should be taken in the morning, at midday and in the evening.

Duration of use
If symptoms worsen or persist after 7 days, a doctor or qualified healthcare practitioner should be consulted.

The product should not be used for more than 2 weeks.
The use in children under 12 years of age is not recommended (see Section 4.4 Special warnings and precautions for use)

4.3 Contraindications
Hypersensitivity to the active ingredient, ivy leaf or to any of the excipients.

4.4 Special warnings and precautions for use
Do not exceed the stated dose.
The use of this product in children under 12 years of age is not recommended because data are not sufficient and medical advice should be sought.
Concomitant use with antitussives such as codeine or dextromethorphan is not recommended without medical advice.

Caution is recommended in patients with gastritis or gastric ulcer.

If dyspnoea, fever or purulent sputum occurs, a doctor or a qualified healthcare practitioner should be consulted. If symptoms worsen or persist for more than 7 days, a doctor or a qualified healthcare practitioner should be consulted. Contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed.

4.6 Pregnancy and lactation
The safety of this product during pregnancy and lactation has not been established, therefore the use of this product 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
Allergic reactions (urticaria, skin rash, dyspnoea) and gastrointestinal reactions (nausea, vomiting, diarrhoea) have been reported. The frequency is not known.

If other adverse side effects not mentioned above occur, a doctor or a qualified healthcare practitioner should be consulted.

4.9 Overdose
Ingestion of significantly higher amounts (more than three times the daily dose) may lead to nausea, vomiting, diarrhoea and excitation. Symptomatic and supportive measures 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 reproductive toxicity, genotoxicity and carcinogenicity have not been performed.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Potassium sorbate
Anhydrous citric acid
Xanthan gum
Cherry flavour
Sorbitol liquid 70% (crystallising)
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Unopened:
3 years
Opened:
3 months.

6.4 Special precautions for storage
No special precautions for storage.

6.5 Nature and contents of container
100 ml / 200 ml in glass bottle
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Diapharm Regulatory Services GmbH
Würzburger Straße 3
D-26121 Oldenburg
Germany

8 MARKETING AUTHORISATION NUMBER(S)
THR 33518/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/02/2011

10 DATE OF REVISION OF THE TEXT
28/02/2011
DiaCough
Cough Syrup

Ivy leaf extract

Patient Information Leaflet

Read all of this leaflet carefully because it contains important information for you. This medicine is available without prescription. However, you still need to use DiaCough Cough Syrup as directed to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor or qualified healthcare practitioner if your symptoms worsen or do not improve after 7 days.
- 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.

What is in this leaflet:

1. What DiaCough Cough Syrup is and what it is used for
2. Before you take DiaCough Cough Syrup
3. How to take DiaCough Cough Syrup
4. Possible side-effects
5. How to store DiaCough Cough Syrup
6. Further information

1. WHAT DIA COUGH COUGH SYRUP IS AND WHAT IT IS USED FOR

This product is a traditional herbal medicinal product containing ivy leaf extract.

It is a traditional herbal medicinal product used to relieve chesty coughs associated with the common cold based on traditional use only.

2. BEFORE YOU TAKE DIA COUGH COUGH SYRUP

Do not take DiaCough Cough Syrup
- If you are allergic (hypersensitive) to the active ingredient, ivy leaf or to any of the excipients of DiaCough Cough Syrup (see section 6).
- If you are under 12 years old.

Consult your doctor or qualified healthcare practitioner before taking this medicine if
- you have gastritis (inflammation of lining of stomach) or have a gastric ulcer (stomach ulcer)
- you are already taking a medicine to help stop you coughing, such as codeine or dextromethorphan.

If you have difficulty breathing, have a fever or bloody phlegm, consult your doctor or qualified healthcare practitioner.

Taking other medicines

Studies investigating the effects of DiaCough Cough Syrup on other medicines have not been performed. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

Pregnancy and breast-feeding:

Ask your doctor or pharmacist for advice before taking any medicine. The safety of this product during pregnancy and breast-feeding has not been established, therefore the use of this product during pregnancy and breast-feeding is not recommended.

Important information about some of the ingredients of DiaCough Cough Syrup:

This medicine contains sorbitol. See section 6.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE DIA COUGH COUGH SYRUP

For oral use only.
Always take DiaCough Cough Syrup exactly as described in this leaflet.
Do not exceed the stated dose.
You should check with your doctor or pharmacist if you are not sure. Shake the bottle well each time before use.

The usual dose is:

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults, the elderly, children aged 12 years and over</td>
<td>5 ml three times a day</td>
</tr>
</tbody>
</table>

Take this product with the enclosed measuring cup.
Take one dose in the morning, at midday and in the evening.
This product is not recommended for use in children under 12 years old.
Consult your doctor or qualified healthcare practitioner if your symptoms worsen or if symptoms persist after using the product for 7 days, if shortness of breath, fever or bloody phlegm occur, if side-effects listed in section 4 become serious or if side-effects not listed in section 4 occur.

Duration of use
The product should not be used for more than 2 weeks.

If you take more DiaCough Cough Syrup than you should
If you take more than the recommended dose (more than three times the daily dose), you may experience nausea, diarrhoea, vomiting or feel excitable. In this case speak to your doctor, pharmacist or qualified healthcare practitioner and take this leaflet with you.

If you forget to take this product
Do not take twice the dose but continue to take the usual dose at the usual time.

If you have any questions, or are unsure about anything, please ask your doctor, pharmacist or qualified healthcare practitioner.
4. POSSIBLE SIDE-EFFECTS

Like all medicines, this product may have side-effects, although not everybody gets them. They are listed below.
Allergic reactions, such as skin rash, red itchy skin and shortness of breath; gastrointestinal disorders such as nausea, vomiting and diarrhoea have been reported. There may be a laxative effect due to the ingredient sorbitol.

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

5. HOW TO STORE DIACOUGH COUGH SYRUP

Keep out of the reach and sight of children.

Do not use DiaCough Cough Syrup after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.
After the first opening of the bottle, the product must be used within 3 months.

6. FURTHER INFORMATION

This product is a traditional herbal medicinal product containing ivy leaf extract.

Active ingredient: Each 5 ml of syrup contains 35 mg of extract (as dry extract) from ivy leaf (Hedera helix L.) (5 : 7.5 : 1).
Extraction solvent: ethanol 30 % w/w.

This product also contains the following ingredients:
Potassium sorbate
Anhydrous citric acid
Xanthan gum
Cherry flavour
Sorbitol liquid 70% (crystallising)
Purified water.
Each 5 ml of syrup contains 1926 mg sorbitol.

DiaCough Cough Syrup is a light brown, slightly cloudy syrup. It contains a plant extract as the active ingredient and its colour and taste can therefore occasionally vary. This, however, does not affect the quality of the preparation.

Each pack contains 100 or 200 ml of syrup.
Not all pack sizes may be marketed.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicine no longer required. These measures will help to protect the environment.

Registration holder:
Diapharm Regulatory Services GmbH
Würzburger Straße 3
D-26121 Oldenburg
Germany
Telephone: +49(0)441-98344-0
Email: info@diapharm.de

Manufacturer of the product:
HÅLSA Pharma GmbH
Maria-Goepert-Straße 1
D-23562 Lübeck
Germany
c/o HÅLSA Pharma GmbH

This leaflet was prepared in October 2010.

You can help to make medicines safer by reporting any side-effect 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).
LABELLING

Label:

DiaCough Cough Syrup

Active ingredient:
Each 5 ml of syrup contains 35 mg of extract (as dry extract) from ivy leaf (Hedera helix L.). Extraction solvent ethanol 30% w/w. Contains sorbitol.

IVY LEAF EXTRACT

For oral use only.
Shake bottle well before use.
Adults, the elderly, children aged 12 years and over: take 5 ml of oral liquid using the enclosed measuring cup 3 times daily.
The syrup should be taken in the morning, at midday and in the evening.
Read enclosed leaflet before use.

The contents of the bottle may be used for 3 months after first opening.

Keep out of sight and reach of children

THR number: 33518/0004
THR holder:
Diapharm Regulatory Service GmbH
Würnburger Straße 3, D-26121 Oldenburg, Germany

100 ml
ET1500000

LOT EXP