Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Diapharm Plantain Cough Syrup

THR 42340/0028

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Diapharm Plantain Cough Syrup

THR 42340/0028

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Diapharm GmbH & Co. KG a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Diapharm Plantain Cough Syrup (Traditional Herbal Registration number: THR 42340/0028) on 06 September 2018. Diapharm Plantain Cough Syrup is available without prescription and can be obtained from pharmacies and non-pharmacy outlets.

Diapharm Plantain Cough Syrup is a traditional herbal medicinal product used to relieve a sore throat and associated dry cough, based on traditional use only. The active ingredient in Diapharm Plantain Cough Syrup comes from the leaves of the Ribwort Plantain plant.

This registration is based exclusively upon the longstanding use of Ribwort Plantain 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.

Diapharm Plantain Cough Syrup

THR 42340/0028

SCIENTIFIC DISCUSSION

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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Diapharm GmbH & Co. KG a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Diapharm Plantain Cough Syrup (Traditional Herbal Registration number: THR 42340/0028) on 06 September 2018. Diapharm Plantain Cough Syrup is available as general sales list (GSL) product.

The application was submitted according to Article 16.c of Directive 2001/83/EC, as amended, as part of the Traditional Herbal Medicines Registration Scheme. Diapharm Plantain Cough Syrup is a traditional herbal medicinal product used to relieve a sore throat and associated dry cough based on traditional use only.

The data supplied by the applicant demonstrates 30 years of traditional use of Ribwort Plantain leaf in the European Community. A satisfactory review of the available safety data on Ribwort Plantain leaf has also been provided, together with an Expert Safety Report supporting the proposed product.

PHARMACEUTICAL ASSESSMENT

HERBAL SUBSTANCE: **RIBWORT PLANTAIN**
Latin name of the plant: *Plantago lanceolata* L.
Plant family: Plantaginaceae

Manufacture of Herbal Substance
The herbal substance is produced from dry leaf of *Plantago lanceolata* L.

The Ribwort Plantain plant is cultivated in Poland and Germany. The plants are harvested between June and September, before flowering. The cultivated plants are treated with 'minimal' pest control management (pesticides, herbicide, fungicide) and fertilisation. The leaves are harvested mechanically. They are cleaned and dried mechanically at 40^0C.

During storage, they are treated with CO_2 under pressure. A statement is provided from the supplier that no other chemical fumigants are used during storage of the raw material other than exposure in closed bags to CO_2. It is considered that CO_2 is an inert gas that does not leave any residue in the treated product.

The herbal substance is produced and collected in accordance with Good Agricultural and Collection Practice (GACP) guidelines. The material is dried in controlled conditions which minimises the risk of polycyclic aromatic hydrocarbons (PAH) accumulating. Representative samples have been analysed and that the material is cleared from the risk of pyrrolizidine alkaloids.

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 current legislation relating to plastic materials and articles intended to come into contact with foodstuffs.

Stability of Herbal Substance
Stability studies have been performed in accordance with current guidelines. The data provided are acceptable and support the proposed re-test period.

HERBAL PREPARATION: **RIBWORT PLANTAIN EXTRACT**

Drug extract ratio (DER): 1:1
Extraction solvent: Ethanol 25% v/v

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. The manufacture of the herbal preparation is considered a standard procedure.

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
An appropriate container closure system is used to store the herbal preparation.

Stability of Herbal Preparation
Stability studies have been performed in accordance with current guidelines. The proposed re-test period and storage conditions for the herbal preparation are acceptable.

HERBAL PRODUCT: **DIAPHARM PLANTAIN COUGH SYRUP**

Description and Composition of Herbal Product
The herbal product is a syrup that is a red liquid with characteristic odour. 10 ml (12.6 g) of syrup contain 1012 mg of extract (as liquid extract) from Ribwort Plantain leaf (*Plantago lanceolata* L. folium) (DER 1:1). The syrup also contains sucrose, blackcurrant flavour (concentrate), potassium sorbate, citric acid monohydrate and purified water.

The compatibility of the herbal preparation with the excipients is demonstrated by the stability testing results. All the excipients are controlled in line with their respective Ph Eur monograph with the exception of the blackcurrant flavour which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis are provided for all excipients.

Manufacture of Herbal Product
A flow diagram outlining the various stages of the manufacturing process and the in-process controls is provided.

In-process controls are appropriate considering the nature of the product and method of manufacture.

Control of Herbal Product
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
The syrup is stored in 120 ml and 200 ml brown glass bottles with white HDPE screw caps. A polypropylene measuring spoon with a 2.5 ml and 5 ml graduation is included in the carton.

Suitable specifications have been provided by the packaging suppliers and it has been confirmed that all primary packaging materials comply with current 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 3 years for the unopened bottle, with no special storage conditions, is appropriate. The in-use shelf life of the product is 3 months after first opening with the storage conditions ‘store below 25 °C. Store in the original container.’

Pharmaceutical Expert
The Quality Overall Summary has been written by an expert with suitable 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-CLINCIAL 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.

The data supplied by the applicant for the proposed THR is sufficient to demonstrate 30 years of traditional use within the European Community as required for registration under the Traditional Herbal Medicines Product Directive.

The non-clinical issues are fully addressed in the Committee on Herbal Medicinal Products (HMPC) assessment report and European Herbal Monograph for Ribwort Plantain leaf.

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 proposed indication is:

"A traditional herbal medicinal product used to relieve a sore throat and associated dry cough based on traditional use only."

The indication is acceptable.

POSOLOGY AND METHOD OF ADMINISTRATION

The applicant has proposed the following:

"For oral use only

Shake the bottle before use

Adults, the elderly, children over 12 years of age: Using the measuring spoon provided, take two 5 ml spoonfuls (10 ml), 3 - 4 times per day

The use is not recommended in children under 12 years of age (see 4.4 Special warnings and precautions for use).

Duration of use:
If the symptoms worsen, or persist longer than 7 days, 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 to show that the medicinal product in question, or a corresponding product, has been in medicinal use throughout a period of at least 30 years, including at least 15 years within the EU.

The applicant has provided a bibliographic review as evidence of the use of Ribwort Plantain within the EU for a period exceeding 30 years. In addition, the Committee on Herbal Medicinal Products (HMPC) assessment report and community monograph for Ribwort Plantain Leaf adequately cover the evidence for traditional use of the herbal preparation 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 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. In addition, the HMPC assessment report for Ribwort Plantain leaf covers the bibliographic safety data available.

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
New non-clinical data are generally not required for an application of this type. The Applicant has provided appropriate genotoxicity testing which concluded that the extract in the product under assessment caused no signs of mutagenic effects in the *Salmonella Typhimurium* Reverse Mutation Assay (in vitro).

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

The applicant has provided a bibliographic review which shows ample evidence for the use of Ribwort Plantain leaf within the EU for a period exceeding 30 years.

A satisfactory review of the safety data has been provided.

Furthermore, the HMPC Herbal monograph and Assessment Report for Ribwort Plantain leaf adequately cover the evidence for traditional use of the extract in the product under assessment for at least 30 years and the safety issues associated with Ribwort Plantain leaf.

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 Certificate may be granted.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling Diapharm Plantain Cough Syrup is presented below:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING – CARTON

1. NAME OF THE MEDICINAL PRODUCT

Diapharm Plantain Cough syrup

2. STATEMENT OF ACTIVE SUBSTANCE(S)

10 ml (12.6 g) of syrup contains 1012 mg of extract (as liquid extract) from Ribwort Plantain leaf (*Plantago lanceolata* L. folium) (DER 1:1).
Extraction solvent: ethanol 25% (V/V).

3. LIST OF EXCIPIENTS

Also contains sucrose and ethanol. See enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Syrup
120 ml / 200 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Directions for use

For oral use only.
Shake the bottle well before use.
Read the enclosed package leaflet before use.

Adults, the elderly & children over 12 years of age:
Using the measuring spoon provided, take two 5 ml spoonfuls (10 ml) of syrup three to four times daily (in the morning, at midday, in the evening and before bed if taking four times a day).

Do not take more than the label tells you to

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
Do not take if you are
- allergic to any of the ingredients in this medicine (listed in section 6 of package leaflet).
- pregnant or breast feeding
- under 12 years of age
- taking any other medicines known to interact with alcohol e.g. metronidazole

This product contains alcohol. If affected, do not drive or use machines.

If symptoms worsen, or do not improve after 7 days consult your doctor.

8. EXPIRY DATE

EXP
After first opening of the bottle, any unused contents must be discarded after 3 months

9. SPECIAL STORAGE CONDITIONS

This product does not require any special storage precautions before opening.

After first opening store below 25 C.

Store in the original container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

THR holder:
Diapharm GmbH & Co. KG
Hafenweg 18-20
48155 Münster
Germany

12. MARKETING AUTHORISATION NUMBER(S)

THR 42340/0028

13. BATCH NUMBER

LOT

14. INSTRUCTIONS ON USE

A traditional herbal medicinal product used to relieve a sore throat and associated dry cough, based on traditional use only.

15. INFORMATION IN BRAILLE

[Nationally approved name]

Certification Mark

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING – BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Diapharm Plantain Cough Syrup

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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Extraction solvent: ethanol 25% (V/V).

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