Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

EM Pharma Marshmallow Cough Syrup

THR 45296/0004

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EM Pharma Marshmallow Cough Syrup

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Gemi Pharma Ltd a Traditional Herbal Registration Certificate for the traditional herbal medicinal product EM Pharma Marshmallow Cough Syrup (Traditional Herbal Registration number: THR 45296/0004) on 06 September 2018. EM Pharma Marshmallow Cough Syrup is available without prescription and can be obtained from pharmacies and non-pharmacy outlets.

Marshmallow Cough Syrup is a traditional herbal medicinal product used for the relief of symptoms associated with a dry, irritating cough, based on traditional use only. The active ingredient in Marshmallow Cough Syrup comes from the root of the Marshmallow plant.

This registration is based exclusively upon the longstanding use of Marshmallow root 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.

EM Pharma Marshmallow Cough Syrup

THR 45296/0004

SCIENTIFIC DISCUSSION

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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Gemi Pharma Ltd a Traditional Herbal Registration Certificate for the traditional herbal medicinal product EM Pharma Marshmallow Cough Syrup (Traditional Herbal Registration number: THR 45296/0004) on 06 September 2018. EM Pharma Marshmallow 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. EM Pharma Marshmallow Cough Syrup is a traditional herbal medicinal product used for the relief of symptoms associated with a dry, irritating cough, based on traditional use only.

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

PHARMACEUTICAL ASSESSMENT

HERBAL SUBSTANCE: **MARSHMALLOW ROOT**
Latin name of the plant: *Althaea officinalis* L.
Plant family: Malvaceae

Manufacture of Herbal Substance
The herbal substance is produced from peeled or unpeeled, cut, dried root of *Althaea officinalis* L.

The Marshmallow plant is cultivated in Europe (including Poland). The use of mineral fertilisation, herbicides, insecticide and fungicides are adopted. The roots are gathered mechanically and manually in the autumn, before flowering. They are then washed and dried naturally or under heat below 40^0C. These are stored in paper bags at room temperature in a dry area with no sunlight. During storage, the roots are treated by fumigation (CO_2 under pressure).

The herbal substance is produced and collected in accordance with Good Agricultural and Collection Practice (GACP) guidelines. It is confirmed that irradiation is not used.

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
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 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: **MACERATE OF MARSHMALLOW ROOT**

Drug extract ratio (DER): 5:36
Extraction solvent: Mixture: purified water, ethanol 96% (47.9:1)

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. 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
The herbal preparation is manufactured in the exact amount needed for the finished herbal product and it is used immediately after production. Therefore, no container has been described.

Stability of Herbal Preparation
The extract is used immediately following manufacture and hence no stability studies have been undertaken.

HERBAL PRODUCT: **EM PHARMA MARSHMALLOW COUGH SYRUP**

Description and Composition of Herbal Product
The herbal product is a syrup that is a viscous, clear liquid with a characteristic smell and taste. Each 10 ml (13.1 g) of syrup contains 4.71 g of macerate from Marshmallow root (*Althaea officinalis* L., radix) (DER 5:36). The syrup also contains purified water, ethanol and benzoic acid (excipients of the herbal preparation) and sucrose and benzoic acid (E 210) [excipients of the herbal product].

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. 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. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Control of Herbal Product
A satisfactory specification with appropriate tests and limits has been provided for the herbal product.

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

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

Container Closure System
The syrup is stored in brown glass bottles or brown polyethylene terephthalate bottles with an aluminium screw cap with gasket made of polyethylene and is supplied with a measuring cup with 2.5 ml to 15 ml scale graduations. The bottle is packed into a carton and is available in a pack size of 95 ml (125g).

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 the storage conditions 'Do not store above 25ºC. Keep the bottle in the outer carton in order to protect from light', is appropriate. The in-use shelf life of the product is 28 days after first opening.

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 Committee on Herbal Medicinal Products (HMPC) assessment report for *Althaea officinalis* L. radix provides a full review of non-clinical data available and concludes that Marshmallow root is generally safe.

An assurance has been provided that appropriate genotoxicity testing will be carried out, in accordance with the European guideline on the assessment of genotoxicity of herbal substances/preparations (EMEA/HMPC/107079/2007).

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 for the relief of symptoms associated with a dry, irritating cough, based on traditional use only."

The indication is acceptable.

POSOLOGY AND METHOD OF ADMINISTRATION

The applicant has proposed the following:
"**Dosage:**
For oral use only.

Adults, elderly & children over 12 years of age:
Using the measuring cup provided take 10 mls every 4 to 6 hours a day.
Repeat the dose depending on the symptoms up to a maximum of 4 times a day.

Maximum daily dose: 40mls
The use in children under 12 years of age is not recommended (See Section 4.4 'Special warnings and precautions for use.').

Duration of use:
Do not use for more than 7 days.

If symptoms worsen, or do not improve after 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 Marshmallow root within the EU for a period exceeding 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.

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. An assurance has been provided that appropriate genotoxicity testing will be carried out, in accordance with the European guideline on the assessment of genotoxicity of herbal substances/preparations (EMEA/HMPC/107079/2007).

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 satisfactory evidence for the use of Marshmallow root within the EU for a period exceeding 30 years.

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 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 for EM Pharma Marshmallow Cough Syrup is presented below:

SCALE 1:1
DIMENSIONS 105X 49MM

EMPHARMA

Marshmallow Cough Syrup

Marshmallow Root Macerate

95 ml

A traditional herbal medicinal product used for the **relief of symptoms associated with a dry, irritating cough**, based on traditional use only.
Dosage for oral use only
Adults, the elderly & children over 12 years: Using the measuring cup provided, take 10 mls every 4 to 6 hours a day. Repeat the dose depending on the severity of symptoms up to a maximum 4 times a day. If required, up to a maximum of 4 doses (40mls) can be taken per day. Do not use for more than 7 days. Do not use if under 12 years, pregnant or breast feeding. Do not take more than the label tells you to.
Ingredients: Each 10ml (13.1 g) of syrup contains 4.71 g of macerate from Marshmallow root (*Althaea officinalis* radix) (DER 5:36) Extraction solvent: water : ethanol (47.9:1). Also contains: sucrose and ethanol.
PLEASE READ THE ENCLOSED LEAFLET BEFORE YOU TAKE THIS MEDICINE. Keep out of the sight and reach of children. Do not store above 25°C. Keep the bottle in the outer carton to protect from light. Discard the syrup 28 days after first opening the bottle.
THR HOLDER: Gemi Pharma Ltd; Unit 2A, Old Dalby Trading Estate, Old Dalby, Leicestershire, LE14 3NJ, UK.
THR: 45296/0004

LOT:

EXP: