Buttercup Bronchostop Cough Syrup

THR 16467/0001

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The Medicines and Healthcare products Regulatory Agency (MHRA) granted JensonR Plus Limited a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Buttercup Bronchostop Cough Syrup (Traditional Herbal Registration number: THR 41188/0003) on 27 January 2014. The product underwent a change of ownership to Kwizda Pharma GmbH (THR 16467/0001) on 7 March 2014. Buttercup Bronchostop Cough Syrup is available without prescription and can be bought from pharmacies and other outlets.

The active ingredients in Buttercup Bronchostop Cough Syrup come from thyme (Thymus vulgaris L. and Thymus zygis L.) herb and marshmallow (Althaea officinalis L.) root. Buttercup Bronchostop Cough Syrup is a traditional herbal medicinal product used for the relief of coughs, such as chesty coughs and dry, tickly, irritating coughs and catarrh, based on traditional use only.

This registration is based exclusively upon the longstanding use of thyme herb and marshmallow root as traditional herbal medicines 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.
BUTTERCUP BRONCHOSTOP COUGH SYRUP

THR 16467/0001

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal medicine Buttercup Bronchostop Cough Syrup (THR 41188/0003) to JensonR Plus Limited on 27 January 2014. The product underwent a change of ownership to Kwizda Pharma GmbH (THR 16467/0001) on 7 March 2014. 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 for the relief of coughs, such as chesty coughs and dry, tickly, irritating coughs and catarrh, based on traditional use only.

There is sufficient evidence to demonstrate use of thyme herb and marshmallow root 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 thyme herb and marshmallow root has also been provided, together with an Expert Safety Report supporting the proposed product.
HERBAL SUBSTANCE: THYME HERB

Scientific name of the plant: *Thymus vulgaris* L. or *Thymus zygis* L.
Family: Lamiaceae
Common name of the plant: Thyme

The thyme herb is cultivated and is mechanically harvested. After harvesting, the herb is sieved, cleaned, and dried in warm air. No pesticides are used to treat this herbal substance. There is controlled use of chemical fertilisers.

Control of Herbal Substance
An appropriate specification based on the European Pharmacopoeia monograph for thyme is applied and is acceptable. The specification is supported by the batch data provided.

Container Closure System
No data are needed.

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.

HERBAL PREPARATION: THYME HERB DRY EXTRACT

Extract solvent: Water
Drug extract ratio: 7-13:1

Manufacture
A satisfactory description of the manufacturing process of the herbal preparation and flow diagram have been provided. The in-process controls are satisfactorily detailed.

Suitable specifications and/or 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 the 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 thyme herb dry extract is acceptable.

**HERBAL SUBSTANCE:** MARSHMALLOW ROOT

Scientific name of the plant: *Althaea officinalis* L.
Family: Malvaceae
Common name of the plant: Marshmallow

The marshmallow root is collected from the wild. After harvesting, the root is washed and dried naturally. No fumigants are used to treat this herbal substance.

**Control of Herbal Substance**
An appropriate specification based on the European Pharmacopoeia monograph for marshmallow root is applied and is acceptable. The specification is supported by the batch data provided.

**Container Closure System**
No data are needed.

**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.

**HERBAL PREPARATION:** MARSHMALLOW ROOT LIQUID EXTRACT

**Extract solvent:** Water
**Drug extract ratio:** 1:12-14

**Manufacture**
A satisfactory description of the manufacturing process of the herbal preparation and flow diagram have been provided. The in-process controls are satisfactorily detailed.

Suitable specifications and/or 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**
A satisfactory description of the container closure system has been provided.

**Stability**
The extract is used immediately following manufacture and so no stability studies have been undertaken. This is acceptable.

**HERBAL PRODUCT: BUTTERCUP BRONCHOSTOP COUGH SYRUP**

**Description and Composition of the Herbal Product**
Buttercup Bronchostop Cough Syrup is a viscous, brown-red liquid oral syrup. 15 ml of syrup contains 120 mg of thyme herb dry extract, 830 mg of marshmallow root liquid extract and the excipients maltodextrin, acacia (E414), xylitol (E967), methyl parahydroxybenzoate (E218) and purified water (from the herbal preparations) and raspberry juice concentrate, xylitol (E967), methyl parahydroxybenzoate (E218), xanthan gum, citric acid monohydrate, propyl parahydroxybenzoate (E216), purified water and raspberry aroma flavouring (synthetic and natural flavourings, propylene glycol [E1520]).

The compatibility of the herbal preparations with the excipients is demonstrated by the stability testing results. The raspberry juice concentrate and the raspberry aroma flavouring are controlled according to in-house specifications. All other excipients are controlled in line with their respective Ph Eur monographs and representative Certificates of Analysis are provided to demonstrate full compliance with the Ph Eur.

**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.

**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 brown glass bottles (hydrolytic class III) with a tamper evidence ring, nozzle and polyethylene screw cap. A polypropylene measuring cup (with a 2.5 ml to 20 ml scale) is also provided. Pack sizes of 120 ml, 200 ml and 240 ml have been authorised, although not all pack sizes may be marketed.
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 when the product is
unopened, and 4 weeks after first opening, is appropriate when the storage precautions
‘Do not store above 25° C’, ‘Store the bottle in the original package in order to protect
from light’ and ‘Close the bottle tightly after use’ are applied.

**Pharmaceutical Expert**
The Quality Overall Summary has been written by an expert with suitable experience.

**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.

**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 overview submitted in support of this application is satisfactory. The published HMPC assessment reports and Community Monographs for thyme herb and marshmallow root adopted by the HMPC adequately support the non-clinical safety of the herbal preparations.

Due to a shortage of published data on thyme herb and marshmallow root, 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.

Tests on genotoxicity have been performed with different thyme herb extracts and thyme essential oil as well as with a marshmallow root dry extract. No mutagenicity was observed in the tests conducted. Tests on reproductive toxicity and carcinogenicity have not been performed.

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 for the relief of coughs, such as chesty coughs and dry, tickly, irritating coughs and catarrh based on traditional use only.”

The indication is acceptable.

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

“For oral use only.

Adults, the elderly and children over 12 years:
Using the measuring cup provided, 15 ml of syrup to be taken every 4 hours, 4 times per day.
If required, up to a maximum of 6 doses (90ml) can be taken per day.

Method of administration:
Buttercup Bronchostop Cough Syrup may be administered undiluted or diluted in water or warm tea.
This product is not recommended for use in children under 12 years of age (See ‘Section 4.4 Special warnings and precautions for use.’)

Duration of use:
If symptoms worsen, or persist 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 (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 published HMPC assessment reports and Community Monographs for thyme herb and marshmallow root adopted by the HMPC adequately cover the evidence for traditional use of the herbal preparations in the EU for at least 30 years. The requirements of the Directive are considered to be met.
SAFETY REVIEW
Article 16 c 1 (d) requires the applicant to provide a bibliography of the safety data together with an expert report.

The HMPC assessment reports for thyme herb and marshmallow root cover the bibliographic data available and the safety of thyme herb and marshmallow root has been demonstrated. The SmPC is in line with the HMPC Community Monographs.

ASSESSMENT OF SUITABILITY FOR GSL STATUS
No assessment is required as thyme herb and marshmallow root are already included on the General Sales List for oral use.

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
The results of genotoxicity testing were provided and the results were satisfactory. The published HMPC assessment reports and Community Monographs for thyme herb and marshmallow root adopted by the HMPC adequately cover the non-clinical safety issues.

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

The published HMPC assessment reports and Community Monographs for thyme herb and marshmallow root adopted by the HMPC adequately cover the evidence for traditional use of thyme herb and marshmallow root in the EU for at least 30 years and the clinical safety issues associated with thyme herb and marshmallow root.

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.
SUMMARY OF PRODUCT CHARACTERISTICS

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

Bottle labels:

120 ml:

Read the package leaflet before use.
For oral use.

Dosage:
Adults, the elderly and children over 12 years: Using the measuring cup provided, 15 ml of syrup to be taken every 4 hours, 4 times per day.
If required, up to a maximum of 6 doses (90ml) can be taken per day.
Do not give to children under 12 years.
DO NOT EXCEED THE STATED DOSE.

Ingredients:
Each 15ml of oral syrup contains the active ingredients: 120mg of extract (as dry extract) from Thyme herb, 830mg of extract (as liquid extract) from Marshmallow root. Extraction solvent: water.
Also contains: Methyl parahydroxybenzoate and propyl parahydroxybenzoate.
See leaflet for further information.
Keep out of the sight and reach of children.
Do not store above 25°C. Store in the original package. Close tightly after use. After opening use within 4 weeks.
THR Holder: Kwenda Pharma GmbH
THR 16467/0001

200 ml:

Read the package leaflet before use.
For oral use.

Dosage:
Adults, the elderly and children over 12 years: Using the measuring cup provided, 15 ml of syrup to be taken every 4 hours, 4 times per day.
If required, up to a maximum of 6 doses (90ml) can be taken per day.
Do not give to children under 12 years.
DO NOT EXCEED THE STATED DOSE.

Ingredients:
Each 15ml of oral syrup contains the active ingredients: 120mg of extract (as dry extract) from Thyme herb, 830mg of extract (as liquid extract) from Marshmallow root. Extraction solvent: water.
Also contains: Methyl parahydroxybenzoate and propyl parahydroxybenzoate.
See leaflet for further information.
Keep out of the sight and reach of children.
Do not store above 25°C. Store in the original package. Close tightly after use. After opening use within 4 weeks.
THR Holder: Kwenda Pharma GmbH
THR 16467/0001

240 ml:

Read the package leaflet before use.
For oral use.

Dosage:
Adults, the elderly and children over 12 years: Using the measuring cup provided, 15 ml of syrup to be taken every 4 hours, 4 times per day.
If required, up to a maximum of 6 doses (90ml) can be taken per day.
Do not give to children under 12 years.
DO NOT EXCEED THE STATED DOSE.

Ingredients:
Each 15ml of oral syrup contains the active ingredients: 120mg of extract (as dry extract) from Thyme herb, 830mg of extract (as liquid extract) from Marshmallow root. Extraction solvent: water.
Also contains: Methyl parahydroxybenzoate and propyl parahydroxybenzoate.
See leaflet for further information.
Keep out of the sight and reach of children.
Do not store above 25°C. Store in the original package. Close tightly after use. After opening use within 4 weeks.
THR Holder: Kwenda Pharma GmbH
THR 16467/0001