IPAR

Public Assessment Report for a
Traditional Herbal Medicinal Product
for Human Use

Buttercup Bronchostop Day & Night Oral Solution

TR2006/002/001
TR Holder Kwizda Pharma GmbH

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I. INTRODUCTION

Specific provisions were introduced for traditional herbal medicinal products (THMPs) in accordance with the Traditional Herbal Medicinal Products Directive (2004/24/EC). The national regulations, the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007) which implement this Directive came into force on 23 July 2007. Consequently, the Health Products Regulatory Authority (HPRA) has established the Traditional Herbal Medicinal Products Registration Scheme.

Based on the review of the data on quality, safety and traditional use, the HPRA, on 26 February 2021, granted Kwizda Pharma GmbH a Certificate of Traditional Use Registration for Buttercup Bronchostop Day & Night Oral Solution, containing dry extracts of marshmallow root, lime flower and ribwort plantain. This Certificate of Traditional Use Registration was subsequently transferred to Chefaro Ireland DAC on 21 May 2021.

This public assessment report concerns the MR-procedure IE/H/1181/001/MR, for Buttercup Bronchostop Day & Night Oral Solution, with Ireland acting as Reference Member State and the Netherlands as the only Concerned Member State.

This application is for a traditional herbal medicinal product as defined by Article 16a(1) of Directive 2001/83/EC as amended and was submitted as part of the Traditional Herbal Medicinal Product Registration Scheme.

The Summary of Product Characteristics (SmPC) for this traditional herbal medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Buttercup Bronchostop Day & Night Oral Solution
Name(s) of the active substance(s) (INN)	Dry extracts of marshmallow root, lime flower and ribwort plantain
Pharmacotherapeutic classification (ATC code)	R05X
Pharmaceutical form and strength(s)	Oral solution
Traditional Herbal Registration Number in Ireland (TR number)	TR2006/002/001
Traditional Herbal Registration Holder	Kwizda Pharma GmbH
MRP/DCP Number	IE/H/1181/001/MR
Reference Member State	Ireland (IE)
Concerned Member State	Netherlands (NL)

II. QUALITY ASPECTS

This application is for Buttercup Bronchostop Day & Night Oral Solution. The active ingredients of Buttercup Bronchostop Day & Night Oral Solution are dry extracts obtained from marshmallow root, lime flower and ribwort plantain.

II.1 S.1 Herbal Substance

The herbal substances are *Althaea officinalis* L., radix (Marshmallow root), *Tilia cordata* Miller, *Tilia platyphyllos* Scop., *Tilia* × *europaea* L. or their mixtures, flos (Lime flower) and *Plantago lanceolata* L., folium (Ribwort plantain leaf), all of which are described in the European Pharmacopoeia and produced in accordance with the principles of good agricultural and collection practice (GACP).

The herbal substance specifications are considered adequate to control the quality and meet current pharmacopoeial requirements. Batch analytical data demonstrating compliance with these specifications have been provided.

II.2 S.2 Herbal preparation

The herbal preparations are dry extracts of marshmallow root, lime flower and ribwort plantain and are manufactured in accordance with the principles of good manufacturing practice (GMP).

The herbal preparation specifications are considered adequate to control the quality and meet current pharmacopoeial requirements. Batch analytical data demonstrating compliance with these specifications have been provided.

II.3 Medicinal product

P.1 Composition

The composition of the medicinal product is stated in sections 2 and 6.1 of the SmPC. A description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of GMP at suitably qualified manufacturing sites.

The manufacturing process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. with the exception of the flavour, which is adequately controlled by the manufacturer's specifications.

P.5 Control of the Finished Product

The finished product specification is based on the pharmacopoeial monograph for liquid preparations for oral use and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging materials comply with Ph. Eur. and/or EU legislation on materials intended for use with foodstuffs.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Conclusion on quality

The important quality characteristics of the product are well defined and controlled. Satisfactory pharmaceutical documentation has been provided, assuring consistent quality of Buttercup Bronchostop Day & Night Oral Solution.

III. NON-CLINICAL ASPECTS

The HPRA has been assured that good laboratory practice (GLP) standards were followed in an appropriate manner for the Ames test submitted to support the application.
An expert report on safety has been provided which includes an appropriate review of the available literature. Overall, the information presented demonstrating traditional use is considered acceptable and the lack of provision of a complete standard safety package is in line with the EMA 'Guideline on Non-clinical Documentation for Herbal Medicinal Products in Applications

for Marketing Authorisation (bibliographical and mixed applications) and in Applications for Simplified Registration' (EMEA/HMPC/32116/05).
In tests on genotoxicity (Ames tests) with marshmallow root dry extract, lime flower dry extract and ribwort plantain leaf dry extract no mutagenicity was observed with and without metabolic activation. Tests on developmental and reproductive toxicity and carcinogenicity have not been performed. Non-clinical data reveal no special hazard for humans when Buttercup Bronchostop Day & Night Oral Solution is used as indicated.
An environmental risk assessment is not required for herbal medicinal products according to guidance CPMP/SWP/4447/00.

IV. CLINICAL ASPECTS

Buttercup Bronchostop Day & Night Oral Solution is a traditional herbal medicinal product used *in adults and adolescents aged 12 years and older for the symptomatic treatment of throat irritation and dry cough, associated with common cold.*

The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

IV.1 Clinical Efficacy

There is no requirement under the Traditional Herbal Registration Scheme to prove scientifically that the product is efficacious, the registration is based exclusively upon the longstanding use of Buttercup Bronchostop Day & Night Oral Solution as a traditional herbal medicine and not upon data generated from clinical trials.

Article 16c1(c) of Directive 2001/83/EC 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. With regard to this traditional use data, the requirements of Article 16c1(c) have been met.

The efficacy of this traditional herbal medicinal product is plausible on the basis of long standing use and experience.

The indication proposed for Buttercup Bronchostop Day & Night Oral Solution is in line with traditional indications recorded and hence, compatible with the requirements of the Traditional Herbal Medicinal Products Directive 2004/24/EC.

IV.2 Clinical Safety

In accordance with Article 16c1(d) the applicant has provided a bibliographic review of the safety data together with an expert report.

Buttercup Bronchostop Day & Night oral solution is contraindicated in patients with hypersensitivity to marshmallow root, lime flower, ribwort plantain or to any of the excipients listed in section 6.1.

It is indicated for oral short-term use only.

Due to the partly physical and local mode of action of the medicinal product, it is recommended to refrain from drinking for 30 minutes to 1 hour after intake.

Absorption of concomitantly administered medicines may be delayed. As a precautionary measure, this medicinal product should not be taken 30 minutes to 1 hour before or after taking other medicines.

If dyspnoea, high fever or purulent sputum occurs, a doctor should be consulted.

If the symptoms persist, worsen or do not improve after 7 days use of Buttercup Bronchostop Day & Night oral solution, a doctor should be consulted.

The medicine contains 11.04 g of xylitol in the maximum daily dose (60 ml), which may have a laxative effect. Calorific value 2.4 kcal/g xylitol.

The medicinal product contains the preservatives methyl-parahydroxybenzoate and propyl-parahydroxybenzoate. These may cause allergic reactions (possibly delayed).

This medicine contains 13.6 mg of propylene glycol in each 15 ml.

The medicine also contains 0.0018 mg benzyl alcohol in each 15 ml dose. Benzyl alcohol may cause allergic reactions. High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

The use in children under 12 years of age has not been established due to lack of adequate data.

No interaction studies have been performed, however, due to the sedative activity of lime flower, Buttercup Bronchostop Day & Night oral solution may potentiate the sedation induced by CNS depressants such as antihistamines, antidepressants, benzodiazepines, opioids and alcohol.

Due to the mild sedative activity of lime flower, this product may cause drowsiness. If affected, individuals should not drive or operate machinery.

The safety of the product during pregnancy and lactation has not been established.
Buttercup Bronchostop Day & Night Oral Solution is not recommended during pregnancy and in women of childbearing potential not using contraception.
It is unknown whether components of marshmallow root dry extract, lime flower dry extract and ribwort plantain leaf dry extract are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Buttercup Bronchostop Day & Night Oral Solution.

If adverse reactions occur, a doctor or pharmacist should be consulted.

In conclusion, this product proves not to be harmful in the specified conditions of use based on the review of safety data, expert report and additional data provided.

IV.3 Pharmacovigilance

It should be noted that in accordance with Article 16g of Directive 2001/83/EC, as amended, the pharmacovigilance requirements described in Articles 101-108 of Directive 2001/83/EC, as amended, also apply in respect of traditional herbal medicinal products.

V. OVERALL CONCLUSIONS

The important quality characteristics of the product are well defined and controlled. Satisfactory pharmaceutical documentation has been provided, assuring consistent quality of Buttercup Bronchostop Day & Night Oral Solution.

The HPRA, on the basis of the data submitted, considered that Buttercup Bronchostop Day & Night Oral Solution demonstrated adequate evidence of traditional use for the approved indication and no new non-clinical or clinical safety concerns have been identified.

A Certificate of Traditional Use Registration for Buttercup Bronchostop Day & Night Oral Solution is granted.

VI. REVISION DATE

June 2022

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
Transfer	CRN00CX74	SmPC section 7, 8, 10 Package Leaflet	N/A	10/06/2022

		New TR Holder: Kwizda Pharma GmbH New TR number: TR2006/002/001		