**IPAR**

Public Assessment Report for a

# Traditional Herbal Medicinal Product for Human Use

Name of Product: Chanelle ivy leaf syrup

TR0688/001/002

TR Holder: Chanelle Medical

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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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 23rd July 2007. Consequently the Health Products Regulatory Authority (HPRA) has established the Traditional Herbal Medicinal Products Registration Scheme.

The Public Assessment Report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of a Certificate of Traditional Use Registration for a specific traditional herbal medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of EC Directive 2001/83/EC, as amended by Directive 2004/27/EC and Directive 2004/24/EC. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the traditional herbal medicinal product for marketing in Ireland.

Based on the review of the data on quality, safety and traditional use, the HPRA has granted Chanelle Medical a Certificate of Traditional Use Registration for Chanelle Ivy Leaf Syrup and Chanelle Ivy Leaf Lozenges, containing ivy leaf dry ethnolic extract (DER 4-8:1)

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 products | Chanelle Ivy Leaf Syrup<br>Chanelle Ivy Leaf Lozenges |
| Name(s) of the active substance(s) (INN) | ivy leaf dry ethanolic extract (DER 4-8:1) |
| Pharmacotherapeutic classification (ATC code) | R05 |
| Pharmaceutical form and strength(s) | Syrup/ lozenges |
| Marketing Authorisation Number(s) in Ireland (PA) | PA0688/047/002-003 |
| Marketing Authorisation Holder | Chanelle Medical |

## II. QUALITY ASPECTS

### II.1. Introduction

These applications are for Chanelle ivy leaf syrup and lozenges.

### II.1 Herbal substance

The active ingredient of these products is obtained from ivy leaf (*Hedera helix*).
The specifications of this herbal substance are adequate and will meet current pharmacopoeial specifications.

### II.2 Herbal preparation

The herbal preparation is ivy leaf dry extract and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The herbal substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

### II.3 Medicinal product

P.1 Composition

The excipients in the medicinal products are listed in section 6.1 of their respective SmPCs.

A visual description of the products are included in section 3 of their respective SmPCs.

P.2 Pharmaceutical Development

The products are established pharmaceutical forms and their 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 good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the 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 flavourings in the syrup and lozenges. These flavours are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for syrup and lozenges, and the tests and control limits are considered appropriate for these product types.

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 sites 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 respective SmPCs .

Evidence has been provided that the packaging complies with EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

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

### II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Chanelle ivy leaf syrup and lozenges.

## III. NON-CLINICAL ASPECTS

Ivy Leaf is a well-established use medicinal product as defined by Article 10(a) of Directive 2001/83/EC as amended. As such no pharmacological, toxicological or clinical studies have been undertaken, and the nonclinical overview provided is based on bibliographic searches. Due to their heterogeneity and different origin, it cannot be taken as granted that all published studies cited in the report were conducted in accordance with current GLP requirements. However, this is not thought to affect the overall conclusions of the overview.

III.2 Pharmacology

The pharmacology of Ivy Leaf (*Hedera Helix* L., folium) extract is well characterised. The biologically active compounds responsible for the medicinal use of ivy leaves are triterpen saponins; hederacoside C and α-hederin are the predominant substances. No new studies were submitted. The bronchodilating effect of ivy leaf extract has been demonstrated in *in vitro*

experiments and *in vivo* studies. An *in vitro* effect of ▪-hederin on β2-adrenergic receptors could be demonstrated, preventing the internalization of β2-adrenergic receptors on the surface of bronchial smooth muscle cells and alveolar type II cells. As a result, a higher number of β2-adrenergic receptors can be activated by the endogenous ligand adrenaline, thereby increasing β2-adrenergic receptor binding and the formation of cAMP. This results in an increased bronchodilation and secretion of surfactant.
Ivy leaf extract have been demonstrated to possess anti-inflammatory, anti-thrombin, antibacterial, antiviral, antihelmintic and antifungal properties. Ivy leaf extract has also demonstrated hypoglycemic activity in rabbits, and a petroleum ether extract of *H. helix* aerial parts has demonstrated mild anticancer effects on cancer cell lines *in vitro*.

III.3 Pharmacokinetics

No non-clinical pharmacokinetic studies have been conducted. From the available literature, it is assumed that hederasaponins are poorly absorbed following oral administration.

III.4 Toxicology

No new studies were submitted. The applicant has presented non-clinical data from the literature including acute and repeat dose toxicity, genotoxicity, reproductive and developmental toxicity. No carcinogenicity studies are available.

Haemolytic effects were detected in rats after exposures in excess of maximum human exposure.

Embryotoxic effects of α-hederin were reported from experiments in rats following subcutaneous administration, attributed to a resultant drop in the maternal serum zinc concentration.

Mutagenicity studies using α-hederin, β-hederin and δ-hederin isolated from ivy leaf showed no mutagenic potential in the Ames test using *Salmonella typhimurium* strain TA 98.

III.5 Ecotoxicity/environmental risk assessment

An environmental risk assessment is not required for herbal medicinal products according to guidance CPMP/SWP/4447/00. There is no increased environmental risk associated with the introduction of this product.

III.6 Discussion on the non-clinical aspects

Extracts of ivy leaves are used therapeutically in commercially available preparations in Europe for the treatment at common cold associated with cough and symptomatic treatment of acute and chronic inflammatory bronchial disorders. No new non-clinical data have been submitted by the applicant, and further non-clinical studies are not required. The non-clinical overview based on literature review is appropriate and supports the use of ivy preparations in the context of respiratory diseases with cough. Safety during pregnancy and lactation has not been established. In view of the pre-clinical data, and the lack of data in humans, the use of ivy leaf during pregnancy and lactation should be avoided.

## IV. CLINICAL ASPECTS

Chanelle Ivy Leaf Syrup and Lozenges are traditional herbal medicinal products used as an expectorant in case of productive cough exclusively based on long-standing use.

This products are indicated for use in adults and adolescents over 12 years of age.

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 Chanelle Ivy Leaf Syrup and Lozenges 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 Chanelle Ivy Leaf Syrup and Lozenges 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.

These products are for short-term oral use only and the recommended dose should not be exceeded.

Patients are advised to seek the help of a qualified healthcare professional if their symptoms worsen or persist for more than 7 days. Patients who are short of breath, have a high temperature or have phlegm which is yellow green to brown in colour should consult a doctor.

These products should not be used in children under 12 years, pregnant or breast-feeding women or anyone who is allergic to ivy preparations, to plants belonging to the family Araliaceae or to any of the ingredients of these products.

These products may not be suitable for patients who have gastritis or a gastric ulcer.

These products contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

It is not known if these products can affect the ability to drive or use machinery. Users should know how this product affects them before driving or using machinery.

The side effects that may occur when using these products include skin rashes and difficulty breathing. Users should stop taking these products if these side effects occur.

Other side effects which may be experienced by some users of these products include nausea, vomiting and diarrhoea. How often these side effects occur is not yet known.

Overdose can provoke nausea, vomiting, diarrhoea and agitation.

In conclusion, these products prove 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.
The Applicant has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

**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 Chanelle Ivy Leaf Syrup and Lozenges.

The HPRA, on the basis of the data submitted, considered that Chanelle Ivy Leaf Syrup and Lozenges demonstrated adequate evidence of traditional use for the approved indication(s) and no new non-clinical or clinical safety concerns have been identified.

A Certificate of Traditional Use Registration for Chanelle Ivy Leaf Syrup and Lozenges is granted.

**VI. REVISION DATE**

**VII. UPDATES**