IPAR

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

Echinaforce Cold and Flu tablets
Extract (as dry extract) from fresh *Echincea purpurea* (L.) Moench herb and root
TR 2309/009/004
A. Vogel Ireland Limited
Registration date: 5th November 2012

CONTENTS

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 A. Vogel Ireland Limited a Certificate of Traditional Use Registration for Echinaforce Cold and Flu Tablets, containing a dry extract from fresh *Echinacea purpurea* (L.) Moench herb and root.

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.

II. QUALITY ASPECTS

This application is for Echinaforce Cold and Flu Tablets. The active ingredient of Echinaforce Cold and Flu Tablets is a dry extract of a 95:5 mixture of tinctures of the herb and root (respectively) obtained from the fresh *Echinacea purpurea* (L.) Moench plant. The genus *Echinacea* belongs to the family *Asteraceae*.

II.1 S.1 Herbal Substance

There are two herbal substances in Echinaforce Cold and Flu tablets: *Echinacea purpurea* herba (purple coneflower herb) and *Echinacea purpurea* radix (purple coneflower root). The herbal substance specifications are considered adequate to control the quality and meet current appropriate requirements. Batch analytical data demonstrating compliance with the specifications have been provided.

II.2 S.2 Herbal preparation

There are two herbal preparations in Echinaforce Cold and Flu tablets: *Echinacea purpurea* herb tincture and *Echinacea purpurea* root tincture. The herbal preparations are manufactured in accordance with the principles of good manufacturing practice (GMP). The herbal preparations are mixed together in a 95:5 mixture herb:root prior to the production of the dry extract.

The herbal preparation specifications are considered adequate to control the quality and meet current appropriate requirements. Batch data demonstrating compliance with the 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.

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 standard and is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

All ingredients comply with their respective Ph. Eur. monographs.

P.5 Control of the Finished Product
The Finished Product Specification is based on the pharmacopoeial monograph for tablets 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 components comply with Ph. Eur. or EU food contact legislation requirements.

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 Echinaforce Cold and Flu Tablets.

III. NON-CLINICAL ASPECTS

Echinaforce Cold and Flu Tablets is a traditional herbal medicinal product as defined by Article 16a(1) of Directive 2001/83/EC as amended.
Given the type of application and limited data available, it is not possible to assess if the entire safety package for the phytochemical constituents of Echinaforce Cold and Flu Tablets are acceptable to the standards of today's GLP and safety testing requirements. However, with respect to new studies performed by the applicant, the HPRA has been assured that GLP standards were followed in an appropriate manner in the studies conducted.

A number of new non-clinical studies have been submitted with respect to potential pharmacokinetic drug interactions and genotoxicity. An expert report on safety has been provided with respect to these studies which includes an appropriate review of the available literature. Of the data presented, no safety concern was identified.
Overall the information presented demonstrating traditional use is considered to be 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).

An environmental risk assessment is not required for herbal medicinal products according to guidance CPMP/SWP/4447/00.

IV. CLINICAL ASPECTS

This is a national application submitted by A. Vogel Ireland Limited under Article 16a of Directive 2001/83/EC, as amended.

Echinaforce Cold and Flu Tabletsis a traditional herbal medicinal product used to relieve common cold and flu-like symptoms. This is exclusively based on 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 Echinaforce Cold and Flu Tabletsas 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 Echinaforce Cold and Flu Tablets 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.

This product is intended for short-term use only. The recommended dose should not be exceeded. If high temperature occurs or if symptoms persist, worsen or do not improve after 10 days use of Echinaforce Cold and Flu tablets, a qualified healthcare professional e.g. a doctor or pharmacist should be consulted.

The use of Echinacea in children below 12 years of age is not recommended because a safe use has not been sufficiently documented.
It is recommended that Echinaforce Cold and Flu tablets should not be used in cases of known allergy to the active substance, to plants of the Asteraceae (Compositae) family or to any of the excipients.

Echinacea can trigger allergic reactions (e.g. rash, hives, Stevens-Johnson Syndrome, swelling of the skin, difficulty breathing, asthma and anaphylactic shock) in allergy-prone patients.

Because of their effects on the immune system, Echinacea extracts must not be used in cases of progressive systemic disorders (tuberculosis, sarcoidosis), autoimmune diseases (e.g. collagenoses, multiple sclerosis), immunodeficiencies (e.g. HIV infection, AIDS), immunosuppression (e.g. oncological cytostatic therapy, history of organ or bone marrow transplant) and diseases of the white blood cell system (e.g. agranulocytosis, leukaemias).

This product should not be used at the same time as other medications affecting the immune system.
Echinaforce Cold and Flu tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should also not take this medicine.
There is limited information about the use of Echinaforce Cold and Flu tablets in pregnant women. In the absence of enough information, the use in pregnancy and breast-feeding is not recommended.

Patients may find that when they take Echinaforce Cold and Flu tablets that they feel tingling, irritation or numbness of the mouth. This is due to the presence of alkylamides which are a natural part of the plant extracts in Echinaforce Cold and Flu tablets.

An association with some autoimmune diseases (e.g. multiple sclerosis, erythema nodosum, low blood platelet count, Evans Syndrome, Sjögren syndrome with kidney dysfunction) has also been reported.

There have been no cases of overdose reported with Echinacea products.

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 Echinaforce Cold and Flu Tablets.

The HPRA, on the basis of the data submitted, considered that Echinaforce Cold and Flu tablets 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 Echinaforce Cold and Flu Tablets is granted.

VI. REVISION DATE

March 2019

VII. UPDATES

Scope
Changes (Safety/Efficacy/Pharmacovigilance) to Human and Veterinary Medicinal Products: Other Variation Changes

Change No. - B.I.a.2.A, B.I.a.4.z x 2, B.I.a.1.z x 2, B.I.b.1.C, B.I.b.1.B x 2, B.I.b.1.z x 4, B.I.b.1.g x 2, B.I.b.2.A x 10, B.I.b.2.E x 6, B.I.b.1.F, B.I.b.1.D, B.I.b.1.C, B.I.b.1.B x 2, B.II.a.3.B.1, B.II.b.3.A x 8, B.II.b.5.B x 2, B.II.b.3.z, B.II.b.5.z x 9, B.II.d.1.z, B.II.d.1.C, B.II.d.1.z, B.II.d.2.D

Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/non approval
CRN 2188412	SPC section 4.8	26/01/2017	02/03/2017	Approved
CRN 2189321	SPC section 2	15/02/2017	13/07/2017	Approved