# IPAR

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

Echinaforce Sore Throat Spray
Tinctures from fresh *Echinacea purpurea* (L.) Moench herb and root and tincture from fresh Sage leaves
TR 2309/013/001
A. Vogel Ireland Limited
Date of Registration: 24th April 2015

## CONTENTS

I. INTRODUCTION

II. QUALITY ASPECTS

III. NON-CLINICAL ASPECTS

IV. CLINICAL ASPECTS

V. OVERALL CONCLUSIONS

VI. REVISION DATE

VII. UPDATES

## 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 Ltd a Certificate of Traditional Use Registration for Echinaforce Sore Throat Spray, containing tinctures of fresh *Echinacea purpurea* (L.) Moench herb, fresh *Echinacea purpurea* (L.) Moench root and fresh Sage leaves (*Salvia officinalis* (L.) folium).

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 Sore Throat Spray. The active ingredients of Echinaforce Sore Throat Spray are extracts (tinctures) obtained from fresh *Echinacea purpurea* (L.) Moench herb, fresh *Echinacea purpurea* (L.) Moench root and fresh Sage leaves (*Salvia officinalis* (L.) folium) using ethanol as the extraction solvent.
Each 2 spray dose contains:
• 379.9 mg of tincture from fresh *Echinacea purpurea* (L.) Moench herb (1:12-13). Extraction solvent: ethanol 65% V/V

• 20.0 mg of tincture from fresh *Echinacea purpurea* (L.) Moench root (1: 11-12). Extraction solvent: ethanol 65% V/V
• 189.2 mg of tincture from fresh Sage leaves (*Salvia officinalis* (L.) folium) (1:17-18). Extraction solvent: ethanol 68% V/V
1 spray ≅ 0.22 ml

## II.1 S.1 Herbal Substance

There are three herbal substances in Echinaforce Sore Throat Spray:

- *Echinacea purpurea* herba (herb)
- *Echinacea purpurea* radix (root) and
- *Salvia officinalis* (L.) folium (Sage leaves).

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 three herbal preparations in Echinaforce Sore Throat Spray:

- tincture from fresh *Echinacea purpurea (L.)* Moench herb (1:12-13)
- tincture from fresh *Echinacea purpurea (L.)* Moench root (1:11-12)
- tincture from fresh *Salvia officinalis (L.) folium* (Sage leaves) (1:17-18)

The herbal preparations 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 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 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 excipients comply with their respective Ph. Eur. monographs, apart from sucrose laurate (E473) and soy lecithin which are adequately controlled by the manufacturer's specifications.
All excipients are from non-animal and non-human sources, and, therefore, pose no TSE risk.

P.5 Control of the Finished Product

The Finished Product Specification is satisfactory. The tests and control limits are justified with respect to conventional pharmaceutical requirements and 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 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 SmPC.
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.

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 Sore Throat Spray.

## III. NON-CLINICAL ASPECTS

Echinaforce Sore Throat Spray is a traditional herbal medicinal product as defined by Article 16a(1) of Directive 2001/83/EC as amended.

An expert report on safety has been provided which includes an appropriate review of the available literature.

The Echinaforce extract contained in Echinaforce Sore Throat Spray has been shown to be non-mutagenic in a *Salmonella typhimurium* reverse mutation assay up to a dose of 5000 mcg/plate. The Sage extract contained in Echinaforce Sore Throat Spray has also been shown to be non-mutagenic in a *Salmonella typhimurium* reverse mutation assay up to a dose of 5000 mcg/plate.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed with Echinaforce Sore Throat Spray.

Given the type of application and limited data available, it is not possible to assess if the safety package for the phytochemical constituents of Echinaforce Sore Throat Spray are acceptable to the standards of today's GLP and safety testing requirements. However, it can be concluded that 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 Ltd under Article 16a of Directive 2001/83/EC, as amended.

Echinaforce Sore Throat Spray is a traditional herbal medicinal product used to relieve sore throats associated with coughs, colds and flu-like illnesses, exclusively based on long-standing use. This product is indicated for use in adults and older people over 18 years.

### 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 Sore Throat Spray 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 Echinaforce Sore Throat Spray 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. The important safety information relevant to this product is as follows.

The use of this product in persons below 18 years of age is not recommended because a safe use has not been sufficiently documented.

The recommended dose should not be exceeded.

This product should not be used for more than 7 days. If symptoms worsen during the use of the product or persist for more than 7 days, a doctor or pharmacist should be consulted. Patients should consult a doctor if they have difficulty swallowing or breathing, if their sore throat is severe or is accompanied by high fever, headache, nausea or vomiting.

Because of their immuno-modulatory activity, Echinacea extracts must not be used in cases of progressive systemic disorders (tuberculosis, sarcoidosis), autoimmune diseases (e.g. collagenoses, multiple sclerosis), immunodeficiences (e.g. HIV infections, 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). There is also a possible risk of anaphylactic reactions in atopic patients. Atopic patients should consult their doctor before using Echinacea.

This product contains 40 – 47 vol % ethanol (alcohol). This corresponds to 163 mg alcohol which is equivalent to 4.1 ml beer or 1.7 ml wine per dose (2 sprays). This may be harmful for those suffering from alcoholism. It should be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy. This product should not be used with other medicines known to interact with alcohol (e.g. metronidazole).

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

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

No interaction studies have been performed with this product. This product should not be used at the same time as immunosuppressant medications. The intake of Sage folium preparations might influence the effect of medicinal products acting via the GABA receptor (e.g. barbiturates, benzodiazepines), even if not seen clinically. Therefore use with such medicinal products is not recommended

There are no or limited amount of data from the use of Echinaforce Sore Throat Spray in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Echinaforce Sore Throat Spray is not recommended during pregnancy. There is insufficient information on the excretion of Echinaforce Sore Throat Spray or its metabolites in human milk. A risk to newborns or infants cannot be excluded. Echinaforce Sore Throat Spray should not be used during breast-feeding. Studies on the effects on fertility have not been performed with this product.

No studies on the effects on the ability to drive and use machines have been performed.

This product may cause side effects. These include rash inside the mouth or a burning sensation, skin rash, hives, swelling of the face or skin, blistering of the skin, mouth, eyes or groin, difficulty breathing, asthma or anaphylactic shock.

There have been isolated reports suggesting an association with Echinacea products and autoimmune diseases such as multiple sclerosis, erythema nodosum, low platelet count, Evans syndrome and Sjogren syndrome.

A decrease in the number of white blood cells may occur with long-term use (more than 8 weeks).

Overdose of this product may result in alcohol intoxication. The amount of alcohol in a full bottle (11 g in 30 ml which is equivalent to a small glass of wine) may result in alcohol intoxication and should be treated accordingly.

For Sage leaves overdose has been reported to cause a sense of heat, fast heart rate, vertigo and seizures after an intake corresponding to more than 15 g sage leaves (equivalent to between 38 and 66 doses of this product).

No case of overdose has been reported for Echinacea.

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 Sore Throat Spray.

The HPRA, on the basis of the data submitted, considered that Echinaforce Sore Throat Spray 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 Sore Throat Spray is granted.