**IPAR**

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

A.Vogel Uva-ursi & Echinacea Cystitis oral drops
Tinctures of Bearberry herb and Echinacea purpurea herb

TR2309/021/001
TR Holder A. Vogel Ireland Limited

**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 A.Vogel Uva-ursi & Echinacea Cystitis oral drops, containing an ethanolic tincture of *Arctostaphylos uva-ursi* (L.) Spreng, herba (Bearberry herb) and an ethanolic tincture of *Echinacea purpurea* (L.) Moench, herba (Purple Coneflower herb).

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 A.Vogel Uva-ursi & Echinacea Cystitis oral drops. The active ingredients of A.Vogel Uva-ursi & Echinacea Cystitis oral drops are ethanolic tinctures obtained from fresh *Arctostaphylos uva-ursi* (L.) Spreng, herba (Bearberry herb) and fresh *Echinacea purpurea* (L.) Moench, herba (Purple Coneflower herb).

### II.1 S.1 Herbal Substance

The herbal substances are *Arctostaphylos uva-ursi* (L.) Spreng, herba (Bearberry herb) and *Echinacea purpurea* (L.) Moench, herba (Purple Coneflower herb).

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 an ethanolic tincture obtained from fresh *Arctostaphylos uva-ursi* (L.) Spreng, herba (Bearberry herb) and an ethanolic tincture obtained from fresh *Echinacea purpurea* (L.) Moench, herba (Purple Coneflower herb). 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 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

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/*Ancillary Substances)*

All ingredients comply with Ph. Eur.

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 considered to be sufficiently validated.

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 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 A.Vogel Uva-ursi & Echinacea Cystitis oral drops.

## III. NON-CLINICAL ASPECTS

The HPRA has been assured that the Ames test submitted was conducted in line with OECD guidelines as per EMA guidance

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 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 in Applications for Simplified Registration' (EMEA/HMPC/32116/05).
In the Ames test submitted a positive mutagenic result was reported in Salmonella strain TA98 with or without metabolic activation. The applicant argued this result was likely related to the demonstrated presence of high levels of quercetin in the product used for the analysis. This argumentation is accepted. It should be noted that as such results were not reported in the HMPC monographs of uva ursi or Echinacea purpurea tinctures, it suggests that the components of this product may differ in composition from those analysed for the cited monographs.
However, there is no safety issue anticipated related to this finding (quercetin is not considered toxic to humans at levels likely to be found in this product), and it is known that the presence of quercetin may result in positive Ames test results in herbal medicinal products (EMEA/HMPC/107079/2007).

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

## IV. CLINICAL ASPECTS

A.Vogel Uva-ursi & Echinacea Cystitis oral drops is a traditional herbal medicinal product used to help relieve minor urinary complaints associated with cystitis in women, such as burning sensation during urination and/or frequent urination, 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 A.Vogel Uva-ursi & Echinacea Cystitis oral drops 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 A.Vogel Uva-ursi & Echinacea Cystitis oral drops 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 traditional herbal medicinal product is contraindicated in those with hypersensitivity to the active substances, to plants of the Asteraceae (Compositae) family, to Bearberry or to any of the excipients listed in section 6.1.

Because of their immuno-modulatory activity, Echinacea extracts must not be used in cases of progressive systemic disorders (tuberculosis, sarcoidosis), autoimmune diseases (e.g. collangenoses, 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, leukemias).

This product is also contraindicated in patients with:
- Impaired renal function
- Oedema secondary to heart failure or impaired renal function
- Current or previous kidney disorders
- Conditions where a reduced fluid intake is recommended e.g. severe cardiac or renal disease

This product is contraindicated in pregnancy and lactation.

The use in children and adolescents under 18 years is not recommended because of concerns requiring medical advice.

Patients should not exceed the stated dose.
If complaints or symptoms such as fever, spasms, acute urinary retention, dysuria, urinary incontinence, or blood in urine occur during the use of this product, a qualified healthcare professional e.g. a doctor or pharmacist should be consulted.

There is a possible risk of anaphylactic reactions in atopic patients. Atopic patients should consult their doctor before using Echinacea.

If symptoms persist, worsen or do not improve after 4 days, a qualified healthcare professional e.g. a doctor or pharmacist should be consulted.

The use in men is not recommended because of concerns requiring medical supervision.

Uvae ursi folium may cause a greenish-brown colouration of the urine.

This traditional herbal medicine contains 213 mg of alcohol (ethanol) in each 15 drop dose.

The amount in 15 drops of this medicine is equivalent to less than 6 ml beer or 3 ml wine.
The small amount of alcohol in this medicine will not have any noticeable effects. As it contains alcohol, it should be avoided in patients taking other medicines known to interact with alcohol (e.g. metronidazole).

This traditional herbal medicinal product is not to be used concomitantly with immunosuppressant medications.

Gastrointestinal symptoms (e.g. nausea, vomiting and stomach ache have been reported).
Hypersensitive reactions (rash, urticaria, Stevens-Johnson Syndrome, angioedema of the skin, Quincke edema, bronchospasm with obstruction, asthma and anaphylactic shock) may occur.
Echinacea can trigger allergic reactions in atopic patients. Association with autoimmune diseases (multiple sclerosis, erythema nodosum, immunothrombocytopenia, Evans Syndrome, Sjorgen Syndrome with renal tubular dysfunction) has been reported.

The alkylamides present in A.Vogel Uva-ursi & Echinacea Cystitis oral drops can affect the buccal mucosa which may be experienced as tingling, irritation and numbness in the mouth, this is however considered to be part of the clinical effect.

No case of overdose has been reported. However, overdose of this product may result in alcohol intoxication: the amount of alcohol in a full bottle (21.3 g in 50 ml: equivalent to 2 glasses of wine) may result in intoxication and should be treated accordingly.

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 A.Vogel Uva-ursi & Echinacea Cystitis oral drops.

The HPRA, on the basis of the data submitted, considered that A.Vogel Uva-ursi & Echinacea Cystitis oral drops 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 A.Vogel Uva-ursi & Echinacea Cystitis oral drops is granted.

## VI. REVISION DATE

## VII. UPDATES