LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Läkemedelsverket 2014-12-11

Public Assessment Report
Scientific discussion

Esberitox, tablet

[Dry extract of *Baptisia tinctoria* (L.), radix (wild indigo), *Echinacea pallida* (Nutt.) Nutt., radix (pale coneflower), *Echinacea purpurea* (L.) Moench, radix (purple coneflower), and *Thuja occidentalis* L., herba(white cedar)]

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This module reflects the scientific discussion for the approval of Esberitox, tablet. The procedure was finalised at 2012-06-30. For information on changes after this date please refer to the module 'Update'.

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LAY SUMMARY

The Medical Products Agency (Läkemedelsverket, MPA) has granted Schaper & Brümmer GmbH & Co KG, Germany, a traditional-use registration for the herbal medicinal product Esberitox, tablet. This product is available without prescription and can be bought from pharmacies and other outlets.

Esberitox is traditionally used for the relief of symptoms of common cold. The active ingredient is a dry extract of four different herbal substances: (1) *Baptisia tinctoria* (L.) (baptisia), (2) *Echinacea pallida* (Nutt.) Nutt. (läkerudbeckia), (3) *Echinacea purpurea* (L.) Moench (röd solhatt) and (4) *Thuja occidentalis* L. (tuja).
This registration is based exclusively upon evidence of traditional use of Esberitox as a herbal medicinal product and not upon data generated from clinical trials. For traditional herbal medicinal products there is no requirement to scientifically prove the effect; adequate evidence of traditional use is sufficient.

The chemical/pharmaceutical quality of the product is acceptable and no new or unexpected safety concerns have been identified during the assessment. It was therefore decided that Esberitox could be registered as a traditional herbal medicinal product.

I. INTRODUCTION

Schaper & Brümmer GmbH & Co KG, Germany has applied for a traditional-use registration for Esberitox, tablet. The application was submitted under Article 16a traditional use registration for herbal medicinal product of the Directive 2001/83 EC, as amended.
The application is a national application for Sweden.

The active substance is a dry extract of four different herbal substances: (1) *Baptisia tinctoria* (L.) (baptisia), radix, (2) *Echinacea pallida* (Nutt.) Nutt. (läkerudbeckia), radix (3) *Echinacea purpurea* (L.) Moench (röd solhatt), radix and (4) *Thuja occidentalis* (L.) (tuja), herba.
For approved indications, see the Summary of Product Characteristics.

Esberitox, tablet was first authorised as a natural remedy in 2008-04-30. As a consequence of the new legislation regarding (traditional) herbal medicinal products the product was reclassified as a traditional herbal medicinal product in 2012-06-30.

II. QUALITY ASPECTS

II.1 Introduction

Esberitox is presented in the form of tablet containing 3.2 mg of the active substance, a dry extract of *Baptisia tinctoria* (L.). (wild indigo), radix; *Echinacea purpurea* (L.) Moench (purple coneflower), radix; *Echinacea pallida* (Nutt.) Nutt. (pale coneflower), radix; and *Thuja occidentalis* L. (white cedar), herba, with a mix ratio of (4.92 : 1.85 : 1.85 : 1), which corresponds to approximately 11 mg dry root of wild indigo, 4.0 mg dry root of pale coneflower, 4.0 mg dry root of purple coneflower and 2.2 mg dry leafy twig of white cedar.

The excipients are: lactose monohydrate, sucrose, macrogol and magnesium stearate.

All manufacturers involved in the production operate in accordance with EU-GMP, or where relevant, GACP (Good Manufacturing Practise and Good Agricultural and Collection Practice, respectively).

II.2 Drug Substance

The herbal substances *Echinacea pallida* (Nutt.) Nutt., radix and *Echinacea purpurea* (L.) Moench, radix comply with the monographs pale coneflower root and purple coneflower root in the European Pharmacopoeia and the general monograph for herbal drugs. The other two herbal substances, wild indigo and white cedar do not have monographs in the European Pharmacopoeia. These two herbal substances are instead controlled using in-house specifications and comply with the general monograph for herbal drugs.

The plants used are cultivated in Germany or wild growing plants. Relevant information on growing conditions and controls of the herbal substances (such as residues of heavy metals and pesticides as well as microbiological quality) have been provided.

The herbal substances are mixed in a ratio of (4.92:1.85:1.85:1) and extracted using ethanol 30 % (v/v). After extraction, the liquid extract (1:11) is concentrated, resulting in a soft extract,

which contains the native dry extract and water. For manufacturing reasons, this extract is mixed with excipients evaporated to obtain a granulate.

The manufacturing process has been adequately described and satisfactory specifications have been provided for the starting materials (herbal substances) and excipients/solvents. The tests and limits in the specifications are considered appropriate to control the quality in relation to the intended purpose.

The active substance (herbal preparation) specification includes relevant tests and the limits for impurities have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted.

II.3 Medicinal Product

Esberitox, tablet is formulated using excipients described in the current European Pharmacopoeia. All raw materials used in the product are safe with view to possible TSE/BSE risk.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC.

III. NON-CLINICAL AND CLINICAL ASPECTS

III.1 Introduction

The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has issued Community monographs on *Echinacea purpurea* (L.) Moench, radix, and *Echinacea pallida* (Nutt.) Nutt., radix, whereas *Baptisia tinctoria* L., radix, and *Thuja occidentalis* L., herba, do not have Community monographs. The reader is referred to the Community monographs and the pertinent assessment report for details.

III.2 Non-clinical aspects

The applicant has collected available information from the literature in the areas of non-clinical pharmacology and toxicology. This information has been assessed by the MPA and no signals of non-clinical safety concern have been identified. The exact mechanism of action of the dry extract in relation to its traditional medicinal use cannot be considered clarified.

A product/extract specific study on mutagenic activity has been performed. The extract has been shown not to be mutagenic in Ames test.

Based on the non-clinical information, both from the literature and the product specific study, no objections are raised to the approval of the dry extract as active ingredient in a traditional herbal medicinal product.

III.3 Ecotoxicity/environmental risk assessment

Esberitox is a traditional herbal medicinal product. According to "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00), (traditional) herbal medicinal products are exempted from the obligation to present an environmental risk assessment due to the nature of their constituents.

III.4 Clinical aspects

Results of clinical trials concerning clinical efficacy and safety are not required for the registration of a traditional herbal medicinal product.

III.5 Traditional use

The applicant has provided a bibliographic review which shows sufficient evidence for the medicinal use of Esberitox throughout a period of at least 30 years, including at least 15 years within the Community.

The product itself has been registered as a traditional herbal medicinal product, under the Article 16a of the Directive 2001/83 EC as amended.

III.6 Clinical safety

Conventional clinical safety data are virtually absent. However, longstanding medicinal use and experience of Esberitox have been documented. During this time, no clinical signals that Esberitox is harmful under normal conditions of use have been identified.

Due to insufficient clinical data Esberitox is only recommended for children over 8 years of age.

Due to lack of safety data, the use of products containing Esberitox during pregnancy and lactation is not recommended.

Based on the clinical safety information available, no objections are raised to the approval of Esberitox as a traditional herbal medicinal product.

IV. PRODUCT INFORMATION

The product information (Summary of Product Characteristics, Package Leaflet and labelling) has been assessed and accepted by the Medical Products Agency.

V. OVERALL CONCLUSION, RISK ASSESSMENT AND RECOMMENDATION

For Esberitox, tablet the handling, manufacture and quality control of raw materials, active substance and finished product are in line with GMP and pharmacopoeial requirements. The applicant has shown that the chemical/pharmaceutical quality is acceptable and can confirm that the process is under control and ensures both batch reproducibility and compliance with the product specification.

Esberitox has had a medicinal use for at least 30 years, including at least 15 years within the Community.

No signals of preclinical or clinical safety concern have been identified under normal conditions of use.

Esberitox, tablet can be recommended for registration as a traditional herbal medicinal product.

VI. APPROVAL

Esberitox, tablet was approved in the national procedure on 2012-06-30.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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