LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Läkemedelsverket 2014-10-06

Public Assessment Report

Scientific discussion

Bronwel Comp, oral solution

Thymus vulgaris L./_Thymus zygis_ L., dried herb, dry extract (7-13:1); water
Althaea officinalis L., dried root, liquid extract (1:12-14); water

Asp.no.: 2012-1232

This module reflects the scientific discussion for the approval of Bronwel Comp, oral solution. The procedure was finalised at 29 April 2014. 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 Mimer Medical, Sweden, a traditional-use registration for the herbal medicinal product Bronwel Comp, oral solution. This product is available without prescription and can be bought from pharmacies and other outlets.

The active ingredients of Bronwel Comp are extracts from dried Thyme herb (*Thymus vulgaris* L. and/or *Thymus zygis* L.) and from dried root of Marshmallow (*Althea officinalis* L.). Thyme herb has been used traditionally as an expectorant in cough associated with cold, whereas Marshmallow root has been used traditionally as a demulcent for the symptomatic treatment of oral or pharyngeal irritation and associated dry cough.

This registration is based exclusively upon evidence of traditional use of Thyme herb and Marshmallow root as herbal medicinal products 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 Bronwel Comp, oral solution, could be registered as a traditional herbal medicinal product.

I. INTRODUCTION

Mimer Medical has applied for a traditional-use registration for Bronwel Comp, oral solution. The application was submitted under Article 16a traditional use registration for herbal medicinal products of the Directive 2001/83 EC, as amended.
The application is a national application for Sweden.

The active substances are water extracts from dried Thyme herb (*Thymus vulgaris* L. [garden thyme] /*Thymus zygis* L. [spanish thyme] dried herb; dry extract [7-13:1]; water) and from dried root of Marshmallow (*Althea officinalis* L. [marshmallow] dried root; liquid extract [1:12-14]; water).

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Bronwel Comp is presented in the form of an oral solution. Each ml of the oral solution contains 8 mg dry extract from *Thymus vulgaris* L. and/or *Thymus zygis* L., herba, including 0.17-0.22 mg Thyme oil, as well as 55 mg liquid extract from *Althea officinalis* L., radix. For the manufacture of 1 ml oral solution, 55-102 mg of dried Thyme herb and 4.0-4.6 mg of dried Marshmallow root is used.

The excipients are purified water, xylitol, raspberry juice (concentrated), xanthan gum, maltodextrin, raspberry flavour, citric acid monohydrate, methyl parahydroxybenzoate, propyl parahydroxybenzoate and acacia.

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

II.2 Drug Substance

Herbal drug

The Thyme plants used for production of Bronwel Comp are cultivated in Germany, whereas the Marshmallow plants are collected from the wild in south-eastern European countries. Relevant information on growing conditions and controls of the herbal substance (such as residues of heavy metals and pesticides as well as microbiological quality) has been provided.

The herbal drugs *Thymus vulgaris* L./*Thymus zygis* L.(herb) and *Althea officinalis L.* (root), complies with the requirements of the Ph. Eur. monographs “Thyme, *Thymi herba*” and “Marshmallow root, *Althaeae radix*”, respectively, and the general monograph for herbal drugs.
The analytical methods applied are suitably described and validated.

Herbal preparation

Water is used as extraction solvent when preparing the Thyme extract. During the manufacturing process the essential oil is separated by distillation and thereafter partly restored to the extract, thereby ensuring an amount of 1.5-2 % essential oil in the extract. The genuine extract, *Thymus vulgaris* L./*Thymus zygis* L., dried herb, dry extract (7-13:1), is mixed with maltodextrin and acacia to obtain the manufacturing extract.

Water is used as extraction solvent for the Marshmallow root as well. The genuine extract, *Althaea officinalis* L., dried root, liquid extract (1:12-14), is mixed with methyl parahydroxybenzoate, xylitol and purified water to obtain the manufacturing extract Marshmallow syrup.

The manufacturing process has been adequately described and satisfactory specifications have been provided for excipients and solvents.

The tests and limits in the specifications of the herbal preparations are considered appropriate to control their quality in relation to their intended purpose.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period of the Thyme extract. The Marshmallow syrup is immediately used for production of the medicinal product.

II.3 Medicinal Product

Bronwel Comp, oral solution, is formulated using excipients described in the current European Pharmacopoeia, except for raspberry juice and raspberry flavour, which are controlled according to acceptable in house specifications.

All raw materials used in the product are of vegetable origin, i.e. there should be no risk of transmission of Animal Spongiform Encephalopathy Agents.

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 SmPC, when stored below 25°C.

III. NON-CLINICAL AND CLINICAL ASPECTS

III.1 Introduction

The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has issued one Community monograph on *Thymus vulgaris* L. and/or *Thymus zygis* L., herba, and one Community monograph on *Althaea officinalis* L., radix. There is no Community monograph for the fixed combination.
The reader is referred to the Community monographs and the pertinent assessment reports 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 Thyme and Marshmallow extracts in relation to their traditional medicinal use cannot be considered clarified.

The water extracts of Thyme and Marshmallow have 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 Thyme and Marshmallow extract as active ingredients in a traditional herbal medicinal product.

III.3 Ecotoxicity/environmental risk assessment

Bronwel Comp 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

Bronwel Comp, oral solution, has a traditional use in cough associated with cold, to promote expectoration of viscous mucus and to relieve dry cough and pharyngeal irritation. The applicant has provided a bibliographic review which shows sufficient evidence for the medicinal use of *Thymus vulgaris* L. and/or *Thymus zygis* L., herba, and *Althaea officinalis* L., radix, throughout a period of at least 30 years, including at least 15 years within the Community.

III.6 Clinical safety

Conventional clinical safety data are virtually absent. However, longstanding medicinal use and experience of *Thymus vulgaris* L./*Thymus zygis* L., herba and *Althea officinalis L.* radix, has been documented within the Community. During this time, no clinical signals that neither *Thymus vulgaris* L./*Thymus zygis* L., herba, nor *Althea officinalis L.*, radix, are harmful under normal conditions of use have been identified.

In harmonisation with the recommendations in the Community herbal monographs on *Thymus vulgari*s L. and *Althaea officinalis* L., the use in children under 12 years of age is not recommended.

Due to lack of safety data, the use of Bronwel Comp, oral solution, during pregnancy and lactation is not recommended.

Based on the clinical safety information available, no objections are raised to the approval of Bronwel Comp 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.

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was German.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

V. OVERALL CONCLUSION, RISK ASSESSMENT AND RECOMMENDATION

For Bronwel Comp, oral solution, 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.

The extracts in Bronwel Comp, oral solution, are covered by the Community monographs on *Thymus vulgaris* L./*Thymus zygis* L., herba and *Althea officinalis L.* radix. The applicant has provided a bibliographic review which shows sufficient evidence for the medicinal use of Bronwel Comp throughout a period of 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.

Bronwel Comp, oral solution, can be recommended for registration as a traditional herbal medicinal product.

VI. APPROVAL

Bronwel Comp, oral solution, was approved in the national procedure on 2014-04-29.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Läkemedelsverket 2014-10-06

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
5.4.3-2022-42404 Nat Proc Var II - Quality	The main variation concerns the reduction of the excipient xylitol in the composition. The quantity of xylitol is reduced in order to minimize the risk of adverse effects which are connected to high doses of xylitol (digestive issues, laxative effect). As a consequence of the reduced quantity, other minor adjustments of the composition were necessary, as well as changes in the manufacturing process, changes in analytical methods including product specification, change in the manufacturing process and controls of one of the herbal preparations (marshmallow root extract).	Yes	2022-09-13	Approval	-

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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