

Public Assessment Report

Scientific discussion

Cynaramin, oral drops, solution
(Peumus boldus Molina, folium, liquid extract, (1:10);
Taraxacum officinale Web., radix and herba, liquid extract, (1:17))

Asp. no: 2008-1028

This module reflects the scientific discussion for the approval of Cynaramin. The procedure was finalised on 30 September 2011. For information on changes after this date please refer to the module 'Update'.

LAY SUMMARY

The Medical Products Agency (Läkemedelsverket) has granted Svenska Bioforce AB, Lund, Sweden a traditional-use registration for the herbal medicinal product Cynaramin, oral drops, solution. This product is available without prescription and can be bought from pharmacies and other outlets.

Cynaramin is traditionally used for temporary indigestion with symptoms such as loss of appetite, bloating and flatulence. The active ingredients are two liquid extracts; the first from roots and herb of dandelion (*Taraxacum officinale*, maskros) and the second from leaves of boldo (*Peumus boldo*, boldo). This registration is based exclusively upon evidence of traditional use of boldo and dandelion 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 Cynaramin could be registered as a traditional herbal medicinal product.

I. INTRODUCTION

Svenska Bioforce AB, Lund, Sweden, has applied for a traditional-use registration for Cynaramin, oral drops, solution. 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.

Cynaramin was authorised as a natural remedy (naturläkemedel) in 2005. The topic of the national application is re-classification to a traditional herbal medicinal product.

The active substances are:

Peumus boldus (boldo), leaf, liquid extract, (1:10) ethanol 62 %.

Taraxacum officinale (dandelion) herb and root, liquid extract (1:17) ethanol 43 %.

For approved indications, see the Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

Cynaramin is presented in the form of oral drops, solution containing, per millilitre, 63 mg of the active substance *Peumus boldus* (boldo), leaf, liquid extract, (1:10) ethanol 62 %, which corresponds to approximately 6.3 mg of dried boldo leaves, and 423 mg of the active substance *Taraxacum officinale* (dandelion) herb and root, liquid extract (1:17) ethanol 43 %, which corresponds to approximately 25 mg of fresh root and herb from dandelion.

The excipients are liquid extract of artichoke, liquid extract of peppermint, purified water and anhydrous ethanol.

The product is marketed in glass bottles.

All manufacturers involved in the production operate in accordance with EU-GMP (Good Manufacturing Practice). At the time of approval, GACP (Good Agricultural and Collection Practice) could be confirmed for *Taraxacum officinale*.

II.2 Drug Substance

The herbal substance *Peumus boldus* Molina (boldo), leaf, conforms to the monograph for boldo leaf in the European Pharmacopoeia (Ph. Eur.).

The boldo leaves used for production are collected in South America. 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 leaves are dried and cut before extraction with ethanol (62 %).

The herbal substance *Taraxacum officinale* Web. (dandelion), root and herb, is controlled using an in-house specification.

The dandelion used for production is cultivated in Switzerland and Germany. 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. Fresh plant material is used for the extraction with ethanol (43 %).

Specifications for the active substances dandelion extract and boldo extract (herbal preparations) include 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 and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Cynaramin is a mixture of four extracts, water and ethanol. Two of the extracts (artichoke and peppermint) are excipients. The water and ethanol is of Ph. Eur. quality and the extracts have in-house specifications.

All raw materials used in the product are of vegetable origin.

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.

Total ethanol content in the product is 57 %.

Stability studies under ICH conditions have been performed and data presented support the shelf life and storage conditions claimed in the SmPC.

III. NON-CLINICAL AND CLINICAL ASPECTS

III.1 Introduction

The safety and efficacy of the combination of *Taraxacum officinale*, root and herb, and *Peumus boldus*, leaf, has not yet been evaluated by the Committee on Herbal Medicinal Products (HMPC).

The applicant has collected relevant information from the literature that has been evaluated by the Medical Products Agency (MPA).

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 combination of extracts from *Taraxacum officinale*, root and herb, and *Peumus boldus*, leaf, in relation to its traditional medicinal use cannot be considered clarified.

A product/extract specific study on mutagenic activity has been performed. The extracts 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 combination of ethanolic extracts from *Taraxacum officinale*, root and herb, and *Peumus boldus*, leaf, as active ingredients in a traditional herbal medicinal product.

III.3 Ecotoxicity/environmental risk assessment

Cynaramin is a traditional herbal medicinal product. According to “Guideline on the environmental risk assessment of medicinal products for human use” (EMA/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 medicinal use of the combination of extracts of *Taraxacum officinale*, root and herb, and *Peumus boldus*, leaf, has a long tradition exceeding 30 years in the Community. It has mainly been used for the treatment of digestive complaints, hepatobiliary disturbances and dyspeptic problems.

The applicant has provided a bibliographic review and expert evidence confirming the traditional use of Cynaramin within the Community.

The requirement of traditional use according to Directive 2004/24/EC is considered fulfilled.

III.6 Clinical safety

Longstanding medicinal use and experience of the combination of ethanol extracts of *Taraxacum officinale*, root and herb, and *Peumus boldus*, leaf, has been documented within the Community. During this time, no clinical signals that the combination of active extracts is harmful under normal conditions of use have been identified. In addition, Periodic Safety Update Reports (PSUR) for Cynaramin as a natural remedy support this conclusion. Reported adverse events (allergic skin reactions) are included in the SmPC.

Due to lack of safety data, products containing the combination of ethanolic extracts of *Taraxacum officinale*, root and herb, and *Peumus boldus*, leaf, cannot be recommended for use in children under 12 years of age.

Due to lack of safety data, the use of products containing the combination of ethanolic extracts of *Taraxacum officinale*, root and herb, and *Peumus boldus*, leaf, during pregnancy and lactation is not recommended.

The alcohol content should be taken into consideration when Cynaramin is used by persons with liver disease, epilepsy or alcoholism.

Based on the clinical safety information available, no objections are raised to the approval of Cynaramin 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 Cynaramin, oral drops, solution, the handling, manufacture and quality control of raw materials, active substances 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 combination of extracts in Cynaramin has not been evaluated by the Committee on Herbal Medicinal Products (HMPC) but the applicant has provided evidence that the extracts in Cynaramin have 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.

Cynaramin, oral drops, solution, can be recommended for registration as a traditional herbal medicinal product.

VI. APPROVAL

Cynaramin, oral drops, solution, was approved in the national procedure on 30 September 2011.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
5.4.3-2016-58717	Declaration of active substances, quantities and ethanol content – Concentrations of extraction solvent, total ethanol content in product, DER and quantities of active substances as well as corresponding quantities of herbal drugs were corrected.	SmPC, PIL, Labelling	2017-01-18	Approval	N/A

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