LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Gericomplex, soft capsule

(*Panax ginseng* C.A Meyer., radix, standardised dry extract G115 (3-7:1), ethanol 40%, adjusted to 4 % ginsenosides)

Asp. No: 2008-0437

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

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LAY SUMMARY

The Medical Products Agency (Läkemedelsverket) has granted Boehringer Ingelheim International GmbH, Germany, a traditional-use registration for the herbal medicinal product Gericomplex, soft capsule. This product is available without prescription and can be bought from pharmacies and other outlets.

Gericomplex is traditionally used as a tonic in case of decreased performance such as fatigue and sensation of weakness. The active ingredient is a dry ethanolic extract from underground parts of ginseng (ginseng, *Panax ginseng* C.A. Meyer). This registration is based exclusively upon evidence of traditional use of ginseng 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 Gericomplex could be registered as a traditional herbal medicinal product.

I. INTRODUCTION

Boehringer Ingelheim International GmbH has applied for a traditional-use registration for Gericomplex, soft capsule. 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.

Gericomplex was re-classified to a traditional herbal medicinal product in 2012. Before this the product had been on the market, authorised as a natural remedy, since 1999.

The active substance is *Panax ginseng* C.A. Meyer, radix, standardised dry extract G115 (3-7:1), ethanol 40 %, adjusted to 4 % ginsenosides.

In addition to the active substance, Gericomplex, soft capsule also contains the following ancillary vitamins and minerals:

- retinol palmitate (vitamin A), cholecalciferol (vitamin D_3), DL-α-tocopheryl acetate (vitamin E), thiamine nitrate (vitamin B_1), riboflavin (vitamin B_2), nicotinamide (vitamin B_3), pyridoxine hydrochloride (vitamin B_6), cyanocobalamin (vitamin B_{12}), ascorbic acid (vitamin C), folic acid and biotin.
- ferrous sulphate, dried (iron), zinc sulphate monohydrate (zinc), copper sulphate, dried (copper), manganese sulphate monohydrate (manganese), magnesium sulphate, dried anhydrous (magnesium), calcium hydrogen phosphate, anhydrous (calcium) and sodium selenite, anhydrous (selenium).

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Gericomplex is presented in the form of soft capsules containing 12-22 mg of the active substance "*Panax ginseng* C.A. Meyer, radix, standardised dry extract (3-7:1), ethanol 40 %", which corresponds to approximately 95 mg of dried roots of *Panax ginseng* C.A. Meyer. The extract is adjusted to contain 4 % ginsenosides.

The product also contains, as ingredients with ancillary effects, the following vitamins and minerals:

- 1.48 mg vitamin A, 5.0 microgram vitamin D_3, 10 mg vitamin E, 1.4 mg vitamin B_1, 1.6 mg vitamin B_2, 18 mg vitamin B_3, 2 mg vitamin B_6, 1 microgram vitamin B_{12}, 60 mg vitamin C, 100 microgram folic acid and 150 microgram biotin.
- 10 mg iron, 1 mg zinc, 2 mg copper, 2.5 mg manganese, 10 mg magnesium, 100 mg calcium and 50 microgram selenium.

The excipients are:

Rapeseed oil, gelatin, hard fat, glycerol, lecithin, lactose monohydrate, ethyl vanillin, refined arachis oil, colloidal anhydrous silica, black iron oxide (E 172), red iron oxide (E 712), medium-chain triglycerides, butylhydroxyanisol and butylhydroxytoluene.

The soft capsules are packed in bottles.

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

The herbal substance *Panax ginseng* C.A. Meyer complies with the monograph "ginseng" in the European Pharmacopoeia (Ph. Eur.).

The plants used are cultivated in South Korea, northern China and Canada. 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 roots are cleaned, dried and milled before being extracted with ethanol. The liquid extract is concentrated and dried.

For manufacturing reasons and standardisation, the genuine extract (DER 3-7:1) is mixed with lactose monohydrate and colloidal anhydrous silica to obtain the manufacturing extract (DER 0.9-3.9:1). The extract is adjusted to a total content of ginsenosides (Rb, Rb2, Rc, Rd, Re, Rg1, Rg2 and Rf) of 4 %. The manufacturing process has been adequately described and satisfactory specifications have been provided for starting materials and solvents.

The active substance 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 and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Gericomplex, soft capsule is formulated using excipients described in the current Ph. Eur., except for sodium selenite, lecithin, copper and magnesium which have in-house monographs, red and black iron oxide which conform to Commission Directive 1994/45/EC as well as iron (BP), zinc (USP) and ethyl vanillin (US/NF).
Measures have been taken to minimise the risk of transmitting Animal Spongiform Encephalopathy Agents.
Gelatin used in the product is of bovine origin.
Lecithin is extracted from soya.

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.

III. NON-CLINICAL AND CLINICAL ASPECTS

III.1 Introduction

The safety and efficacy of *Panax ginseng*, radix has not 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 MPA.

The extract in Gericomplex soft capsule, G115, is on the market in Germany since many years as Pharmaton products, on which product specific studies have been performed.

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 *Panax ginseng* 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 an ethanolic extract of *Panax ginseng* as active ingredient in a traditional herbal medicinal product.

III.3 Ecotoxicity/environmental risk assessment

Gericomplex 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 medicinal use of *Panax ginseng,* root has a long tradition exceeding 30 years in the Community. It is mainly used as a tonic in case of decreased performance such as fatigue and sensation of weakness. The recommended dosage of Gericomplex is in the same range as the ones used traditionally and listed in the literature.

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

III.6 Clinical safety

The safety profile of Gericomplex is well established both from clinical studies and from its use for over 30 years as a marketed medicinal product in many countries world-wide with usage by many millions of patients. The majority of adverse events reported are related to gastrointestinal disorders.

Information about the large sales volumes of products containing the G115 extract and a very long history of traditional use indicate that Gericomplex, soft capsule is generally safe.

As no safety data on use in children are available, products containing *Panax ginseng,* root *cannot* be recommended for use in children below the age of 12 years.

Due to lack of safety data, the use of products containing *Panax ginseng,* root during pregnancy and lactation is not recommended.

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

IV. OVERALL CONCLUSION, RISK ASSESSMENT AND RECOMMENDATION

For Gericomplex, soft capsule 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 extract in Gericomplex has not been evaluated by the HMPC but the applicant has provided evidence that the extract in Gericomplex 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.

Gericomplex, soft capsule can be recommended for registration as a traditional herbal medicinal product.

V. APPROVAL

Gericomplex, soft capsule was approved in the national procedure on 30 April 2012.

LÄKEMEDELSVERKET
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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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