LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Hypermin, tablet

[*Hypericum perforatum* L., (St. John's wort) *herba recens*, dry extract (3.1-4.0:1) ethanol 60 %]

Asp. no: 2008-1034

This module reflects the scientific discussion for the approval of Hypermin. The procedure was finalised on 31 January 2012. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

LAY SUMMARY

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

Hypermin is traditionally used in cases of slightly low mood and for minor nervous tension. The active ingredient is an extract from fresh flowering shoots of St. John's wort *(Hypericum perforatum*, johannesört). This registration is based exclusively upon evidence of traditional use of St. John's wort 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 Hypermin could be registered as a traditional herbal medicinal product.

I. INTRODUCTION

Svenska Bioforce AB, Lund, Sweden, has applied for a traditional-use registration for Hypermin, 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.

Hypermin was authorised as a natural remedy (naturläkemedel) in 1998. The topic of the national application is re-classification to a traditional herbal medicinal product.

The active substance is *Hypericum perforatum* L. (St. John's wort, johannesört), *herba recens*, dry extract (3.1-4.0:1), extraction solvent ethanol 60 %.

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

II. QUALITY ASPECTS

II.1 Introduction

Hypermin is presented in the form of tablets containing 40-73 mg dry extract (3.1-4.0:1) of *Hypericum perforatum* L. (St. John's wort), *herba recens*, ethanol 60 %, which corresponds to approximately 0.3-1.3 g of fresh shoots and flowers of St. John's wort or 0.13 - 0.29 g dried shoots and flowers.

The excipients are microcrystalline cellulose, maize starch, soya polysaccharides (Emcosoy®), and hydrogenated cottonseed oil (Lubritab®).

The tablets are filled in amber glass 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 *Hypericum perforatum* L. (St. John's wort), *herba recens* (fresh flowering shoots) is controlled using an in-house specification. The herb is grown 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.

A tincture (DER 1:9) is prepared from the fresh plant material. This intermediate is concentrated to a soft extract to which ethanol and sodium hydroxide are added for preservation, improved homogeneity and neutralisation purposes. Finally, the soft extract is evaporated to a dry extract (DER 3.1-4.0:1), which is considered as the active substance (herbal preparation).

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

Hypermin, tablet, is formulated using excipients described in the current Ph. Eur. (microcrystalline cellulose, maize starch), except for soya polysaccharides (Emcosoy®) and hydrogenated cottonseed oil (Lubritab®), which are controlled according to acceptable in-house specifications. None of the raw materials used in the product are of animal 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.

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 *Hypericum perforatum* (traditional use) have been evaluated by the Committee on Herbal Medicinal Products (HMPC). HMPC concluded that herbal preparations of Hypericum in solid/liquid dosage forms for oral use have both a well-established medicinal and traditional use. However, the extract used in Hypermin was not included in the HMPC monograph.

III.2 Non-clinical aspects

No product-specific studies have been performed. However, the HMPC monograph on *Hypericum perforatum* L., *herba* (traditional use) states that there are no signs of toxic effects. In addition, an adequate literature review of *Hypericum perforatum* was submitted by the applicant. The information was assessed by the MPA and no signals of safety concerns were identified within the areas of non-clinical pharmacology and toxicology.

The exact mechanism of action of *Hypericum perforatum* in relation to its traditional medicinal use cannot be considered clarified.

III.3 Ecotoxicity/environmental risk assessment

Hypermin 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 evidence that extracts of *Hypericum perforatum* have had medicinal use for at least 30 years, of which 15 years within the European Community. Traditional use has been described for the relief of temporary mental exhaustion, symptomatic treatment of minor inflammations of the skin, and symptomatic relief of mild gastrointestinal discomfort.

The requirement of medicinal use for at least 30 years (15 years within the Community) according to Directive 2004/24/EC is considered fulfilled for the extract in Hypermin.

III.6 Clinical safety

Longstanding medicinal use and experience of extracts of *Hypericum perforatum* have been documented within the Community. During this time, no clinical signals that extracts of *Hypericum perforatum* are harmful under normal conditions of use have been identified.

In the assessment report pertaining to the Community monograph on *Hypericum perforatum*, the adverse events observed in clinical trials of Hypericum extracts were stated to have been generally mild and the frequency considerably lower than that observed for standard antidepressants. Periodic Safety Update Reports (PSUR) for Hypermin as a natural remedy support this conclusion. Reported adverse events (gastrointestinal disorders, allergic skin reactions, fatigue, and restlessness) are included in the SmPC.

Hypericum extracts induce the activity of several important drug metabolising enzymes, which may result in interactions with a vast number of drugs resulting in reduced plasma concentrations of the drugs affected. Hence, concomitant use of Hypermin and other drugs is not recommended. The elevated enzyme activity could affect other drugs up to two weeks after cessation of intake of Hypermin.

In the absence of sufficient data, use in children and adolescents under 18 years of age is not recommended.

In the absence of sufficient data, use during pregnancy and lactation is not recommended.

Due to the content of soya polysaccharides (Emcosoy®) as an excipient, Hypermin is contraindicated in patients allergic to peanuts or soya.

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

IV. PRODUCT INFORMATION

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

V. OVERALL CONCLUSION, RISK ASSESSMENT AND RECOMMENDATION

For Hypermin, 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.

It has been adequately documented that the extract in Hypermin has had a traditional medicinal use for at least 30 years, including at least 15 years within the European Community.

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

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

VI. APPROVAL

Hypermin, tablet, was approved in the national procedure on 31 January 2012.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
5.4.3-2015-9985	**Change in composition** – Replacement of maize starch and soy polysaccharides (and removal of soy warnings). **Change in declaration** – "40-73 mg" of extract changed to 66 mg of extract.	SmPC, PIL, Labelling	2015-11-17	Approval	NA
5.4.3-2018-62996	**Change in composition** – Replacement of hydrogenated cottonseed oil with another lubricant: Glycerol distearate.	SmPC, PIL	2018-09-18	Approval	NA

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

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se