LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Flexiloges, film-coated tablet
(*Harpagophytum procumbens* (Burch) DC (devil's claw) dried root, dry extract (4.4-5.0:1) ethanol 60 %)

SE/H/1561/01/MR

This module reflects the scientific discussion for the approval of Flexiloges. The procedure was finalised on 25 May 2009. For information on changes after this date please refer to the module 'Update'.
Please note that the marketing authorisation was first approved with the name "Helaflex" and therefore this product name is used throughout the document.

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LAY SUMMARY

The Medical Products Agency (Läkemedelsverket) has granted Dr Loges & Co GmbH, Winsen, Germany, a traditional-use registration for the herbal medicinal product Helaflex, film-coated tablet. This product is available without prescription and can be bought from pharmacies and other outlets.

Helaflex is traditionally used for the relief of pain and stiffness in cases of mild joint wear (osteoarthritis). The active ingredient is a dry ethanolic extract from roots of devil's claw (*Harpagophytum procumbens* (Burch) DC, djävulsklo). This registration is based exclusively upon evidence of traditional use of devil's claw 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 Helaflex could be registered as a traditional herbal medicinal product.

I. INTRODUCTION

Dr Loges & Co GmbH, Winsen, Germany, has applied for a traditional-use registration for Helaflex, film-coated tablets. 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.

Helaflex 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 substance is *Harpagophytum procumbens* (devil's claw) dried root, dry extract (4.4-5.0:1) ethanol 60 %.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Helaflex is presented in the form of film-coated tablets containing 480 mg of the active substance "*Harpagophytum procumbens* (devil's claw) dried root, dry extract (4.4-5.0:1) ethanol 60 %", which corresponds to approximately 2.3 g of dried devil's claw root.

The excipients are lactose monohydrate, maize starch, microcrystalline cellulose, colloidal anhydrous silica, hypromellose, magnesium stearate, talc, titanium dioxide, macrogols, yellow iron oxide and brown iron oxide.

The film-coated tablets are packed in blisters.

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 *Harpagophytum procumbens* (Burch) DC (devil's claw), root, conforms to the monograph "devil's claw root" in the European Pharmacopoeia (Ph. Eur.).

The herbal substance is cultivated and collected from the wild in the Kalahari region of Africa. 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 cut and dried before extraction with ethanol. Solvents are evaporated to a soft extract. For manufacturing reasons, the genuine extract is mixed with excipients and further dried to obtain a dry extract.

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 and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Helaflex, film-coated tablet, is formulated using excipients described in the current Ph. Eur., except for brown and yellow ferric oxide which conform to a national pharmacopoeia.

All raw materials used in the product are of vegetable origin except lactose monohydrate which is obtained from milk for human consumption. All raw materials 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 and storage conditions 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) issued a Community monograph on *Harpagophytum procumbens* in 2008.
The reader is referred to the Community monograph and the pertinent assessment report for details. The extract contained in Helaflex is equivalent to the extracts described in the monograph.

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 Medical Products Agency (MPA) and no signals of non-clinical safety concern have been identified. The exact mechanism of action of *Harpagophytum procumbens* 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 *Harpagophytum procumbens* as active ingredient in a traditional herbal medicinal product.

III.3 Ecotoxicity/environmental risk assessment

Helaflex 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 *Harpagophytum procumbens* has a long traditional use exceeding 30 years in the Community. It is mainly used in form of liquid or dry extracts for relief of minor articular pain or for the relief of mild digestive disorders (HMPC monograph). The recommended dosage of Helaflex is in the same range as the ones listed in the HMPC monograph and in the literature for relief of minor articular pain.

The applicant has provided sufficient evidence for the traditional medicinal use of *Harpagophytum procumbens* DC, radix throughout a period of at least 30 years, including at least 15 years within the Community.

III.6 Clinical safety

Longstanding medicinal use and experience of ethanolic extracts of *Harpagophytum procumbens*, root has been documented within the Community. During this time, no clinical signals that *Harpagophytum procumbens*, root, is harmful under normal conditions of use have been identified. In addition, Periodic Safety Update Reports (PSUR) for Helaflex as a natural remedy support this conclusion. Non-serious adverse events reported were gastro-intestinal disorders and headache. These adverse events are included in the SPC.

Products containing *Harpagophytum procumbens*, root cannot be recommended for use in children. The Community monograph states that the use in children and adolescents under 18 years of age is not recommended because of the lack of available experience.

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

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

IV. OVERALL CONCLUSION, RISK ASSESSMENT AND RECOMMENDATION

For Helaflex, film-coated 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.

The extract in Helaflex is covered by the Community monograph on *Harpagophytum procumbens*, root. It has thus been adequately documented that the extract in Helaflex 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.
Helaflex, film-coated tablet, can be recommended for registration as a traditional herbal medicinal product.

V. APPROVAL

Helaflex, film-coated tablet was approved in the national procedure on 25 May 2009.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/1561/01/MR	Initial Mutual Recognition Procedure	Yes	2016-05-04	Approval	N/A
SE/H/1561/01/1B/003/G	Change of product name from “Helaflex” to “Flexiloges”	Yes	2020-08-01	Approval	N/A

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

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