LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

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Public Assessment Report
Scientific discussion

Harpatinum, capsule, soft
Harpagophytum procumbens D.C. / H. zeyheri Decne (Devil's claw), radix, dry extract (4.4-5.0:1), ethanol 60 % (V/V)

SE/H/1640/01/DC

ASP no: 2016-1596

This module reflects the scientific discussion for the registration of Harpatinum, capsule, soft. The procedure was finalised on 28th of June, 2017. 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 Florealis ehf, Iceland, a traditional-use registration for the herbal medicinal product Harpatinum, soft capsule. This product is available without prescription and can be bought from pharmacies and other outlets.

Harpatinum is traditionally used for the relief of minor articular pain, and mild digestive disorders such as bloating and flatulence and where there is temporary loss of appetite.
The active ingredient is a dry extract from devil's claw root. This registration is based exclusively upon evidence of traditional use of devil's claw root 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 Harpatinum could be registered as a traditional herbal medicinal product.

I. INTRODUCTION

Florealis ehf. Reykjavík, Iceland has applied for a traditional-use registration of Harpatinum, capsule, soft. The application was submitted under Article 16a traditional use registration for herbal medicinal product of the Directive 2001/83 EC, as amended. The application was submitted as a decentralised procedure with Sweden as reference member state. Concerned member states were Cyprus, Denmark, Finland, Iceland, Malta and Norway.

The active substance is *Harpagophytum procumbens* D.C. / *H. zeyheri* Decne (Devil's claw), radix, dry extract (4.4-5.0:1), ethanol 60 % (V/V).

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

The product is a soft capsule containing the active substance *Harpagophytum procumbens* D.C. / *H. zeyheri* Decne (Devil's claw), radix, dry extract (4.4-5.0:1), ethanol 60 % (V/V).

The excipients are: lactose monohydrate, hydrated colloidal silica, refined soya-bean oil, refined coconut oil, fractionated palm kernel oil, yellow beeswax, purified soya-bean phospholipids, butter fat, gelatin, glycerol, partially dehydrated liquid sorbitol and yellow iron oxide.

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

II.2 Drug Substance

Herbal substance
The herbal substance is *Harpagophytum procumbens* D.C. and/or *H. zeyheri* Decne, radix (Devil's claw root). It complies with the monograph devil's claw root in the European Pharmacopoeia.

The root is collected from the wild and dried naturally. No fumigation or chemical agents are used. 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.

Controls of the herbal substance are according to the European Pharmacopoeia (Ph. Eur.).

Herbal preparation
The herbal preparation *Harpagophytum procumbens* D.C. and/or *H. zeyheri* Decne (Devil's claw) dried root; dry extract (4.4-5:1) ethanol 60 % (V/V), is manufactured by Salus Haus GmbH & Co. KG, Germany. It complies with the monograph Devil's claw root dry extract in the European Pharmacopoeia.

The herbal substance is cut and extracted with ethanol 60 % at room temperature. The liquid extract is concentrated, mixed with excipients (lactose monohydrate and precipitated silicon dioxide) and dried.

The manufacturing process has been adequately described and satisfactory specifications have been provided for starting materials (herbal substance) and excipients/solvents. The tests and limits in the specifications are considered appropriate to control the quality in relation to the intended purpose.

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 have been performed under ICH conditions. The proposed re-test period is 36 months which has been accepted by the RMS.

II.3 Medicinal Product

The finished product is a soft capsule packed in PVC/PVDC-Al blisters. The soft capsules are formulated using excipients described in the current European Pharmacopoeia except for butter fat and fractionated palm kernel oil which are controlled according to in-house monographs and the colouring agent that is controlled according to EU-regulations. All raw materials used in the product 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.

The conditions used in the stability studies are according to the ICH stability guideline. Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has issued a Community monograph on *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne., radix, in 2016. The reader is referred to the Community monograph and the pertinent assessment report for details.

III.2 Pharmacology and Toxicology

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 *Harpagophytum procumbens* 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 *Harpagophytum procumbens / H. zeyheri* as active ingredient in a traditional herbal medicinal product.

III.3 Ecotoxicity/environmental risk assessment

Harpatinum 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Results of clinical trials concerning clinical efficacy and safety are not required for the registration of a traditional herbal medicinal product.

IV.2 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 solid dosage forms for oral use as a traditional herbal medicinal product for "relief of minor articular pain" and "relief of mild digestive disorders such as bloating and flatulence and where there is temporary loss of appetite" (HMPC monograph). The recommended dosage of Harpatinum is in the same range as the ones listed in the HMPC monograph and in the literature.

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

IV.3 Clinical safety

Conventional clinical safety data are virtually absent. However, longstanding medicinal use and experience of *Harpagophytum procumbens*, radix has been documented. During this time, no clinical signals that *Harpagophytum procumbens*, radix is harmful under normal conditions of use have been identified.

As no data on use in children are available, products containing *Harpagophytum procumbens*, radix *cannot* be recommended for use in children below the age of 18 years.

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

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

V. 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
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Harpagophytum Kapseln. The marketing authorisation holder for Harpagophytum Kapseln has confirmed that the product is authorised in Germany, that the readability report was assessed by the German authorities, and that permission is given to Florealis to bridge to the report. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

For Harpatinum, 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 ensure both batch reproducibility and compliance with the product specification.

The extract in Harpatinum is covered by the Community monograph on *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne., radix. It has thus been adequately documented that the extract in Harpatinum 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.

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

VII. APPROVAL

The Decentralised procedure for Harpatinum, soft capsule, was positively finalised on 28th of June, 2017.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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