IPAR

Health Products Regulatory Authority
PUBLIC ASSESSMENT REPORT FOR A TRADITIONAL HERBAL MEDICINAL PRODUCT FOR HUMAN USE

Harpadol
DEVILS CLAW ROOT

TR 1450/1/1
TR holder Laboratoires Arkopharma

I INTRODUCTION

Specific provisions were introduced for traditional herbal medicinal products (THMPs) in accordance with the Traditional Herbal Medicinal Products Directive (2004/24/EC). The national regulations, the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007) which implement this Directive came into force on 23rd July 2007. Consequently the HPRA has established the Traditional Herbal Medicinal Products Registration Scheme.

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authoritys Board (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a Certificate of Traditional Use Registration for a specific traditional herbal medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of EC Directive 2001/83/EC, as amended by Directive 2004/27/EC and Directive 2004/24/EC. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the traditional herbal medicinal product for marketing in Ireland.

Based on the review of the data on quality, safety and traditional use, the HPRA has granted Laboratoires Arkopharma a Certificate of Traditional Use Registration for Harpadol hard capsules, containing 435 mg devil's claw root (*Harpagophytum procumbens D.C. and/or H. zeyheri L. Decne*)

This application was submitted as a standard application according to Article 16c of Directive 2001/83 EC, as amended, as part of the Traditional Herbal Medicinal Product Registration Scheme.

About the product

The genus Harpagophytum belongs to the family Pedaliaceae.The active ingredient of Harpadol is devil's claw root (*Harpagophytum procumbens D.C. and/or H. zeyheri L. Decne*). The product is a clear capsule filled with brown/yellow powder.

Harpadol is a traditional herbal medicinal product used for the relief of minor joint pain in adults over 18 years of age, exclusively based on long-standing use.

There is no requirement under the Traditional Herbal Registration Scheme to prove scientifically that the product is efficacious, the registration is based exclusively upon the long-standing use of Harpadol as a traditional herbal medicine and not upon data generated from clinical trials.

The Summary of Product Characteristics (SmPC) for this traditional herbal medicinal product is available on the HPRA's website.

II QUALITY ASPECTS

This application is for Harpadol hard capsules.

III.1.1 S.1 Herbal Substance

The herbal substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

III.1.2 S.2 Herbal preparation

The herbal substance is to be directly used in the hard capsule following grinding into a powdered form (to make the 'herbal preparation'). As the herbal substance is processed into the powdered form and immediately transferred for use

in the capsule, control, packaging and storage of the herbal preparation is not considered relevant in this case.

III.1.3 Medicinal product

P.1 Composition

The composition of the medicinal product is stated in sections 2 and 6.1 of the SmPC. A description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with the European Pharmacopeia (Ph. Eur).

P.5 Control of Finished Product

The finished product specification is based on the pharmacopoeial monograph for hard capsules, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production sites have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that packaging type complies with Ph. Eur./EU requirements for use with foodstuffs.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

III.1.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Harpadol capsules.

III.1.5 Other information

Not applicable.

III.1.6 Conclusion on quality

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Harpadol.

III NON-CLINICAL ASPECTS

Harpadol is a traditional herbal medicinal product as defined by Article 16a(1) of Directive 2001/83/EC, as amended. Given the type of application and limited data available, it is not possible to assess if the safety standards for the phytochemical constituents of Harpadol are acceptable to the standards of today's GLP and safety testing requirements.

The applicant has performed a bacterial reverse mutation assay with Devil's claw powder contained in Harpadol according to OECD guideline number 471 and in accordance with ICH S2A and the requirements for genotoxicity testing of HMPC as outlined in the Guideline "Assessment of genotoxicity of herbal substances/ preparation" EMEA/HMPC/107079/07. The study was negative, indicating that there is no identified genotoxic concern for Devil's claw. With respect to other potential safety concerns, an expert report on safety has been provided which includes an appropriate review of the available literature. Of the data presented, no safety concern was identified.

No information was provided with respect to carcinogenicity. There is limited information within the literature with respect to the reproductive toxicity potential of Devil's claw. Some evidence suggests that Devil's claw may induce premature labour and therefore should not be used in pregnancy. This information is reflected in sections 4.3, 4.6 and 5.3 of the SmPC and within the package leaflet.

Overall, the information presented demonstrating traditional use is acceptable and thus the lack of provision of a complete standard safety package is acceptable and in line with the EMA "Guideline on Non-clinical Documentation for Herbal Medicinal Products in Applications for Marketing Authorisation (bibliographical and mixed applications) and in Applications for Simplified Registration" (EMEA/HMPC/32116/05).

An environmental risk assessment is not required for herbal medicinal products according to guidance CPMP/SWP/4447/00.

IV CLINICAL ASPECTS

This is a national application submitted by Laboratoires Arkopharma to the Traditional Herbal Medicinal Product Registration Scheme, under Article 16c of Directive 2001/83/EC, as amended by Directive 2004/24/EC.

The proposed indication is: A Traditional Herbal Medicinal Product for the relief of minor joint pain in adults over 18 years of age, exclusively based on long-standing use.

III.3.1 Clinical Efficacy

No clinical efficacy data is required for registration of Traditional Herbal Medicinal Products (THMP). However, Article 16c1(c) requires the applicant to provide bibliographic or expert evidence to show that the medicinal product in question, or a corresponding product, has been in medicinal use throughout a period of at least 30 years, including at least 15 years within the Community.
This traditional use data has been submitted with this application and is satisfactory and is in accordance with Article 16c1(c)

The efficacy of this traditional herbal medicinal product is plausible on the basis of long-standing use and experience.

The indication proposed for Harpadol is in line with traditional indications recorded and hence, compatible with the requirements of the Traditional Herbal Medicinal Products Directive 2004/24/EC.

III.3.2 Clinical Safety

In accordance with Article 16c1(d) the Applicant has provided a bibliographic review of the safety data together with an expert report.

The use of Harpadol should be avoided in those who are allergic to Devil's claw (also known as Harpagophytum) which this product contains and in those allergic to any of the ingredients.

Harpadol is intended for oral short term oral use only. The dosing recommendation of taking one capsule three times daily should not be exceeded**.**

If the condition worsens, new symptoms develop or symptoms persist during the use of Harpadol, or for more than four weeks, a doctor should be consulted.

A doctor should be consulted before taking Harpadol if other symptoms such as swelling, redness of a joint, or fever are present in addition to joint pain.

As a general precaution, patients with gastric or duodenal ulcers should not use Harpadol (Devil's claw)

Harpadol (Devil's claw) is not recommended for use in children and adolescents under 18 years of age due to lack of safety data in this age group.

Some studies in animals have shown that at high concentrations of Devil's claw, possible effects on the heart similar to a medicine called Verapamil can occur. Therefore, those with heart conditions should speak with their doctor before taking Harpadol (Devil's claw)

Safety during pregnancy and lactation has not been established. Therefore, Harpadol should not be used during pregnancy and lactation.

Side effects of Harpadol which have been reported are diarrhoea, nausea, vomiting, abdominal pain, headache, dizziness and allergic skin reactions.

In conclusion, this product proves not to be harmful in the specified conditions of use based on the review of safety data, expert report and additional data provided.

III.3.3 Pharmacovigilance

It should be noted that in accordance with Article 16g of Directive 2001/83/EC, as amended, the pharmacovigilance requirements described in Articles 101-108 of Directive 2001/83/EC, as amended, also apply in respect of Traditional Herbal Medicinal Products.

V OVERALL CONCLUSIONS

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Harpadol.

The HPRA, on the basis of the data submitted, considered that Harpadol demonstrated adequate evidence of traditional use for the approved indication and no new preclinical or clinical safety concerns have been identified.

A certificate of traditional use for Harpadol is granted.