

FLEXIHERB FILM-COATED TABLETS

THR 23056/0001

UKPAR

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FLEXIHERB FILM-COATED TABLETS

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted M H Pharma (UK) Ltd a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Flexiherb Film-coated Tablets (Traditional Herbal Registration number: THR 23056/0001). This product is available without prescription and can be bought from pharmacies and other outlets.

The active ingredient of Flexiherb Film-coated Tablets comes from the roots of the plant *Harpagophytum procumbens*, also known as Devil's claw. Flexiherb Film-coated Tablets is a traditional herbal medicinal product used for the relief of backache, rheumatic or muscular pain, and general aches and pains in the muscles and joints. This registration is based exclusively upon the longstanding use of Devil's claw root as a traditional herbal medicine and not upon data generated from clinical trials. There is no requirement under the Traditional Herbal Registration scheme to prove scientifically that the product works.

No new or unexpected safety concerns arose from this application and it was, therefore, decided that a Traditional Herbal Registration Certificate could be granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal remedy Flexiherb Film-coated Tablets to M H Pharma (UK) Ltd on 26 January 2007. This product has been granted a general sales licence (GSL).

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

The data supplied by the Applicant demonstrate 30 years of traditional use of Devil's Claw in the European Community. A satisfactory review of the available safety data on Devil's claw root has also been provided, together with an Expert Safety Report supporting the proposed product.

PHARMACEUTICAL ASSESSMENT REPORT

I REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

None

II INTRODUCTION

This is a national application submitted by M H Pharma (UK) Ltd, trading as Medic Herb, under the Traditional Herbal Medicines Registration Scheme.

A satisfactory manufacturing licence has been provided by the site responsible for the batch release and manufacture of the finished herbal product.

A satisfactory manufacturing licence has been provided from the herbal substance manufacturer.

There are no current product licences for Devil's claw-based products. One homeopathic product containing Devil's claw was given an automatic Product Licence of Right by the MHRA in 1972. The product is Harpagophytum (PLR 00298/7759), a solution for injection, and the licence was granted to Weleda UK Ltd.

Legal status

A General Sales List status has been granted to this product.

Use

This is a traditional herbal medicinal product for the relief of backache, rheumatic or muscular pain, and general aches and pains in the muscles and joints, based on evidence of traditional use only.

III HERBAL SUBSTANCE

III.A.1 General information

The plant source of the herbal substance Devil's claw root is *Harpagophytum procumbens* De Candolle, belonging to the Pedaliaceae family. It grows in the area surrounding the Kalahari Desert in southern Africa and Namibia.

III.A.2 Manufacture

Description of Manufacturing Process and Process Controls

The plant is perennial. The plant can be collected from the wild or cultivated. In the autumn the underground plant parts are harvested and cleaned. The medicinal parts are the dried tubular secondary roots (cut into slices, pieces or pulverized) and the thick lateral storage roots (cut into small pieces before they dry).

Assurance is provided that the herbal substance is produced in accordance with the principles of Good Agricultural and Collection Practice (GACP).

The specifications of the raw material have been provided, indicating that no pest management and fertilization treatments have been used.

Control of Material

The starting material, Devil's claw root, complies with the monograph "Devil's claw root" (Ph Eur).

III.A.3 Characterisation

The starting material is examined according to the monograph "Devil's claw root" (Ph. Eur.) by macroscopic and microscopic examinations and thin layer chromatography.

Impurities

The purity of the starting material is tested satisfactorily.

III.A.4 Control of Herbal Substance

Specification

The specifications of the herbal substance are provided and are satisfactory.

Analytical Procedures

Certificates of Analysis for the herbal substance have been provided. Tests of identity and assay and all Ph Eur test methods used are stated to comply with the Ph Eur monograph, 5th Edition.

Details of tests for pesticide residues, heavy metals, microbial quality and aflatoxins are provided and are satisfactory.

The suppliers have confirmed that the starting material has not been treated with fumigants. The suppliers have confirmed that the material is not treated with ethylene oxide or irradiation.

III.A.5 Reference Standards or Materials

According to Ph Eur monograph "Devil's claw root".

III.B HERBAL PREPARATION

III.B.1 General information

Herbal preparation: Devil's claw root dry extract De Candolle and/or *Harpagophytum zeyheri* Decne (according to Ph Eur monograph "Devil's claw root")

Parts of the plant used: Dried tubular secondary roots cut into slices or pieces

Name of the herbal substance: Devil's claw root

Extraction solvent: water

III.B.2 Manufacture

A satisfactory description of the manufacturing process of the herbal substance and a flow diagram have been provided.

Control of Materials

Please see section III.A.4.

Controls of Critical Steps and Intermediates

The in-process controls (IPC) and specifications are satisfactorily detailed. There are no critical steps identified as the manufacture of the herbal substance is considered a standard procedure.

III.B.3 Characterisation

Suitable tests for identification and purity are included in the specification.

III.B.4 Control of Herbal Preparation

Specification

Details of the proposed release specification for Devil's claw root dry extract are provided and
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are satisfactory.

Analytical Procedures

Satisfactory details of the analytical methods are provided. .

Validation of Analytical Procedures

Satisfactory validation data are provided (see section IV.5).

Batch Analyses

Satisfactory certificates of analysis (CoA) are provided for three recent batches of the herbal preparation..

Justification of Specification

The identity, purity tests and assay of Devil's claw root dry extract have been adequately justified.

III.B.5 Reference Standards or Materials

Details of reference standards and materials used are provided and are satisfactory. Certificates of Analysis for the internal standards have been provided.

III.B.6 Container Closure System

Specifications for the container closure system have been provided by the supplier, together with the declaration of compliance with Directive 2002/72/EC relating to foodstuffs. Every goods receipt of packaging material is controlled by the drug substance manufacturer.

III.B.7 Stability

Two batches of herbal preparation, stated to be production batches, have been subjected to stability testing in ICH long term, intermediate and accelerated conditions. Stability testing was carried out in the containers proposed for marketing. Satisfactory tests and limits were applied.

The studies have been fully completed for the proposed duration and data have been provided for 36 months in long term conditions (25⁰C/60%RH), 12 months in intermediate conditions and 6 months in accelerated conditions. There has been no significant change in the overall quality of the herbal preparation during the studies in all tested conditions.

The proposed retest period is 36 months. This is acceptable. A stability commitment is given to submit data from a third production batch stored in long term storage conditions following registration.

IV HERBAL PRODUCT

IV.1 Description and Composition of the Herbal Product

Qualitative composition of the herbal product.

Component	Ref std	Function
Herbal substance		
Dry extract of Devil`s claw root Extraction solvent: water		Active ingredient

Other constituents Tablet core: Cellulose, powdered Lactose monohydrate Sodium starch glycolate (Type A) Silica, colloidal anhydrous Magnesium stearate	Ph Eur	Filling agent
	Ph Eur	Filling agent
	Ph Eur	Disintegrant
	Ph Eur	Increase flowability, anti-adhesive
	Ph Eur	'Outer' lubricant
Film coating: Sucrose (Saccharose) Titanium dioxide E 171 <i>Sepifilm LP 010 containing:</i> Hypromellose Microcrystalline cellulose Stearic acid	Ph. Eur	Sweetening agent
	Ph. Eur	Colourant
		Film-forming agent
	Ph. Eur	Film-forming agent
	Ph. Eur	Disintegrant
	Ph. Eur	Moisture-repellant

Type of container:

The film-coated tablets are sealed into binary blisters made of PVC/PVDC and aluminium with 10 tablets each (see also section IV.7).

IV.2 Pharmaceutical Development

The composition of the film-coated tablet is common and the choice of excipients is based on experience. Compatibility of the chosen excipients and the herbal substance is confirmed by stability testing of the herbal product. Manufacture of the herbal product by direct tableting is a standard procedure. The film-coated tablets are sealed into binary blisters made of PVC / PVDC and aluminium foil, which is a commonly used container.

IV.3 Manufacture

Manufacture

The finished product is manufactured at a suitable site, which is also the batch control and release site.

Batch Formula

The qualitative composition of the mixture used in the manufacture of the granulated dry extract is provided and is satisfactory.

Description of Manufacturing Process and Process Controls

A flow diagram outlining the various stages of the manufacturing process and the in-process controls is provided.

The manufacturing process is by normal dry granulation using a commercial compactor. The dry extract is mixed with the excipients and ground. This mixture is compacted, fractionated and filled in a container. On a suitable rotary pelleting machine the tablet mixture is pressed to tablet cores. After tableting the film-coating is carried out following standard procedures in suitable equipment.

Packaging:

The film-coated tablets are sealed into binary blisters, equipped with the package leaflet.

Control of Critical Steps and Intermediates

Satisfactory in-process controls are applied to this product during manufacture.

Process Validation and/or Evaluation

Data of in-process controls from three batches have been provided. The MA holder has committed to perform the process validation on three production scale batches following registration.

IV.4 Control of Excipients

All the excipients and analytical procedures are as specified by the pharmacopoeia monographs. The colouring agent titanium dioxide complies with Directive 2001/50/EC. Certificates of analysis (CoA) of the excipients have been provided by the suppliers. For Sepifilm LP 010, a CoA has been provided by the finished product manufacturer. The only excipient not described in a pharmacopoeia is water used in the manufacture of the herbal extract. Specifications are based on the German Drinking Water Regulations and a CoA has been provided. Water used in the manufacture of the finished product is purified water corresponding to the standards of the Ph. Eur.

Excipients of Human or Animal Origin

Adventitious agents safety evaluation

The supplier has confirmed that the lactose monohydrate is produced from milk acceptable for human consumption. The suppliers of magnesium stearate and *Sepifilm* have provided a satisfactory declaration that the materials are of vegetable origin.

IV.5 Control of Herbal Product

Specification(s)

The release and shelf life specifications of the herbal product are provided and are satisfactory.

Analytical Procedures

Satisfactory details have been provided on all analytical procedures.

Validation of Analytical Procedure

Satisfactory validation of analytical procedures has been carried out.

Batch Analyses

Satisfactory batch data have been provided to support the specifications.

IV.6 Reference Standards or Materials

COAs for the internal standards have been provided. The identity and purity of the compounds have been sufficiently established. The method of assay of the reference substance, harpagoside, is sufficiently validated, and identification is performed.

IV.7 Container Closure System

The film-coated tablets are sealed into binary blisters made of PVC/PVDC-aluminium. The supplier has appropriately provided specifications of the container components. The primary packaging materials comply with Directive 2002/72/EC relating to contact with foodstuffs. Information regarding the frequency and nature of testing by the finished product manufacturer following receipt of the packaging material from the suppliers is satisfactory.

IV.8 Stability

Stability Summary and Conclusion

Three pilot scale batches of more than 10% of the proposed production size were put on stability studies in ICH conditions, under long term (25°C/60%RH), intermediate and accelerated

conditions. Stability testing was carried out in the containers proposed for marketing. The batches are tested according to specifications.

The studies have been fully completed to their proposed durations and data has been provided for 36 months for the long term studies, 12 months in intermediate conditions and 6 months in accelerated conditions. Based on the results a proposed shelf life of 36 months labelled with the statement 'Do not store above 25⁰C is justified.

Post-approval Stability Protocol and Stability Commitment

The applicant has committed to provide long term stability testing of three production batches.

V. ASSESSOR'S COMMENTS ON THE SUMMARY OF PRODUCT CHARACTERISTICS, LABEL AND PATIENT INFORMATION LEAFLET

Summary of Product Characteristics (SPC)

The SPC for this product is satisfactory.

LABELLING

The labelling for this product is satisfactory.

Patient Information Leaflet (PIL)

The PIL has satisfactorily undergone patient user testing and is satisfactory.

Assessor's Overall Conclusions

A grant of a Traditional Herbal Registration is acceptable.

PRECLINICAL ASSESSMENT

I. Introduction

This is a national application submitted by M H Pharma UK (Ltd) trading as Medic Herb under Article 16.c of Directive 2001/83 EC, as amended (Traditional Herbal Medicines Registration Scheme). The product is a tablet for oral use containing dry aqueous extract from Devil's claw root (*Harpagophytum procumbens* DC). One film-coated tablet contains 600 mg of the extract, equivalent to 900 to 1500 mg of dried root.

II. Nonclinical aspects

Preclinical Safety Data

The Safety Expert Report submitted by the applicant lists relevant references to published work studying the acute toxicity, subacute toxicity and chronic toxicity of Devil's claw root.

III. Nonclinical overview

The applicant has submitted an adequate literature review with this application. An Expert Safety Report was also provided, which included reviews of some nonclinical data. The Expert Safety Report was written by a pharmacist with expertise in herbal medicines and is dated 20 of October 2005.

The Nonclinical Overview contains a short review of the nonclinical data for Devil's claw. Some of the studies in the literature review were conducted and published before GLP was a regulatory requirement. Moreover, it is not possible to ascertain if the data assessed in the review would comply with today's regulatory safety testing requirements with regards to design, conduct and analysis.

Due to a shortage of published data on Devil's Claw it is not possible to assess if the safety package for the phytochemical constituents of Devil's Claw meets current standards of GLP and safety testing requirements. However, the information supplied demonstrating traditional use is acceptable and thus the lack of provision of a complete standard safety package is acceptable and in compliance with guideline EMEA/HMPC/32116/0.

In view of the absence of results of genotoxicity testing the applicant has provided assurance that results will be provided before the renewal of the registration.

IV. Summary of product characteristics

The Summary of Product Characteristics for this product is satisfactory.

V. Environmental risk assessment

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

VI. Conclusion

The information supplied demonstrating traditional use of Devils Claw is acceptable. An
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adequate literature review for Devil's Claw has been carried out by the applicant and no new nonclinical data was submitted for assessment with this application. Granting of a THR is acceptable.

CLINICAL ASSESSMENT

INTRODUCTION

This is a national application submitted by M H Pharma UK (Ltd), trading as Medic Herb, under Article 16.c of Directive 2001/83 EC, as amended (Traditional Herbal Medicines Registration Scheme). The product is a tablet for oral use containing dry aqueous extract from Devil's claw root (*Harpagophytum procumbens* DC). One film-coated tablet contains 600 mg of the extract, equivalent to 900 to 1500 mg of dried root.

Devil's Claw products are currently widely available in the UK as herbal remedies exempt from licensing, under Section 12(2) of the Medicines Act 1968. There are currently no Devil's Claw products with marketing authorisations.

The applicant has stated that there are no other applications for the same product in the EEA. No comment has been made about whether this product is available in other countries outside the EEA.

EVIDENCE OF TRADITIONAL USE

Article 16 c 1 (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.

Devil's Claw (*Harpagophytum procumbens* DC) has been used in traditional medicines as a stomachic and a bitter tonic, and for arthritis, gout, myalgia, fibrositis, lumbago, pleurodynia and rheumatic disease. Modern use of Devil's Claw has mainly been concerned with its use in the treatment of rheumatic and arthritic conditions and of lower back pain.

The German Commission E Monograph lists a range of indications, including loss of appetite, dyspepsia and supportive therapy of degenerative disorders of the locomotor system.

The Applicant has provided information to support the traditional use of the product. The information provided is considered satisfactory to demonstrate that Devil's Claw aqueous root extract has been in use for at least 30 years (of which at least 15 have been in an EU member state), and that its use covers the indications sought. The requirements of the directive are therefore satisfied.

PROPOSED INDICATION FOR FLEXIHERB

The indications for this product are as follows:

A traditional herbal medicinal product used for the relief of backache, rheumatic or muscular pain, and general aches and pains in the muscles and joints, based on evidence of traditional use only.

Assessor's comment:

The proposed indications are considered to be in agreement with the traditional uses of Devil's Claw. The proposed indication is considered acceptable for an OTC product and is in line with the wording currently permitted for oral ibuprofen products available OTC which include uses in

'rheumatic or muscular pain and backache'. The product is considered suitable for use without the supervision of a medical practitioner.

SAFETY REVIEW

Article 16 c 1 (D) requires the Applicant to provide a bibliographic review of safety data together with an expert report.

A safety review has been provided and an Expert Safety Report written by a suitably qualified expert who is a pharmacist with expertise in herbal medicines. His CV has also been provided.

The applicant has provided the following summary of the safety review in support of their application:

Summary

This report was prepared to support the registration of Flexiherb Film-coated Tablets under the Traditional Herbal Medicinal Products Directive.

Posology for Flexiherb Film-coated Tablets: 2 to 4 tablets daily of a 600mg dry aqueous extract (1.5- 2.5:1) Devil's claw root. This is equivalent to 1.8 to 6.0 g of dried herb daily.

Evidence of safety:

Phytochemical composition: seven chemical classes have been identified in Devil's claw root. None of the sources of evidence investigated have identified any specific safety issues with these classes of compounds.

Preclinical safety data: pre-clinical toxicity data shows Devil's claw and its constituents to have a low toxicity in acute, subacute and chronic animal studies, whether given by an oral, intraperitoneal, or intravenous route. Pharmacodynamic data from human studies does not identify any clinically significant changes with Devil's claw, except one study which showed a biphasic decrease in basal cysteinyl-leukotriene (Cys-LT) biosynthesis following oral administration of Devil's claw extract (Lowe et al, 2001).

Clinical Safety data: Devil's claw has been contraindicated in the presence of a gastric or duodenal ulcer. With gallstones, it is recommended that advice be sought first from a physician. Some texts contraindicate its use in pregnancy and lactation purely due to lack of data. There is one report of an interaction with *E. purpurea* in the presence of warfarin. No negative effects are reported through overdose, or in the ability to operate machinery.

Undesirable effects:

- Twelve ADR's possibly associated with Devil's claw have been reported to the MHRA. None of these were fatal.
- A summary of 18 systematic investigations of Devil's claw prepared in August 2004 noted no severe ADRs reported in a total study population of 2,219 patients. Mild GI disturbance occurred in 3.5 % of the total population, while mild allergic reactions occurred in 0.31 %. Other mild ADR's occurred in 0.59 % of the total study population.

In conclusion:

Devil's claw and its constituents are well tolerated, with a low toxicity and a low incidence of only mild ADRs. Although the literature states that health risks with Devil's claw are theoretical

(Bone, 2003), the herb is often contraindicated in the presence of a gastric or duodenal ulcer. In addition, with gallstones, it is recommended that advice should be first sought from a physician, and it is not recommended in pregnancy or lactation. Such a safety profile would support the current application of Flexiherb Film-coated Tablets under the Traditional Herbal Medicinal Products Directive.

Assessor's comment:

The active constituents of Devil's Claw have not been definitively established, however, the iridoid glucoside constituents, such as harpagoside, are considered to play an important role and would be classified as 'active markers' i.e. constituents which are generally accepted to contribute to the therapeutic activity.

There are no well-controlled, randomised studies to support the absence of possible interactions of Flexiherb Film-coated Tablets with certain drugs. Therefore, as a precautionary measure, the following is included in section 4.5 *Interaction with other medicinal products and other forms of interaction* of the SPC:

“Drugs that inhibit platelet aggregation, anticoagulants, non-steroidal anti-inflammatory agents (including aspirin and COX-2 inhibitors):

There is a theoretical risk that concomitant administration with Devil's claw may increase the risk of bleeding.”

The use of this product during pregnancy and lactation is an unresolved issue, with some references recommending contraindication because of lack of data. Clearly, this issue is important enough to be addressed properly, and lack of data should not lead to the erroneous assumption that “no undesirable effects are to be expected”. A cautious approach is strongly encouraged until new data to this respect are available.

With regard to clinical safety the applicant has presented a summary of adverse events reported in 18 systematic investigations of Devil's Claw. No severe ADRs were reported in a total study population of 2,219 patients. Mild GI disturbance occurred in 3.5 % of the total population, while mild allergic reactions occurred in 0.31 %. Other mild ADR's occurred in 0.59% of the total study population.

SUMMARY OF PRODUCT CHARACTERISTICS

The SPC for Flexiherb Tablets is satisfactory.

PATIENT INFORMATION LEAFLET

The PIL for Flexiherb Tablets has undergone patient user testing and is satisfactory.

LABELLING

The labelling for this product is satisfactory.

ASSESSMENT OF SUITABILITY FOR GSL STATUS

Section 51 of the Medicines Act 1968 states that “GSL may be appropriate for medicines which can, with reasonable safety, be sold or supplied otherwise than by or under the supervision of a pharmacist”. The term “reasonable safety” may usefully be defined as: “Where the hazard to health and the risk of misuse and the need for special precautions in handling are small, and where wider sale would be a convenience to the purchaser”.

Suitability of indication for GSL:

1. Hazard to health

A review of safety provided (including MHRA’s surveillance data and 18 trials) showed no serious ADRs. Pharmaco-vigilance data gathered on other similar products available without license do not indicate specific health risks associated with the active substance. All the ADRs reported are adequately summarised in the relevant sections of the SmPC. There is still the risk that a patient may use this product instead of another medicine that would be more suitable for their disease, and a warning to this effect is already present in the PIL (advising the patient to consult with a practitioner if deterioration or no improvement is felt at 8 weeks). Considering that the indications are not any life threatening diseases this is acceptable.

2. Risk of misuse

The therapeutic index of this product seems to be high enough. The ADRs reported are mild (including reported allergic reactions). The indication is simple enough to be understood by the general public. Hence, the risk of misuse is felt to be low.

3. Need to take special precautions in handling

There are no special precautions for handling this product.

4. Wider sales are convenient to the purchaser

Current experience with other GSL products sold for the relief of pain of muscles and joints (i.e. paracetamol) indicates this level of accessibility is beneficial to the patients. There is no reason at this point to think that classifying Devil’s Claw as non-GSL would be more convenient to the public than having it as GSL.

In summary, it is considered that the 4 above mentioned criteria have been met and this product should be suitable for GSL status.

DISCUSSION

This is an application for registration under the Traditional Herbal Medicinal Products Directive. The data supplied by the Applicant are sufficient to demonstrate 30 years of traditional use within the Community for corresponding products. A review of the available safety data on Devil’s Claw has been provided, together with an Expert Report supporting the proposed product.

A GSL status can be granted for this product.

OVERALL CONCLUSION AND RISK ASSESSMENT

QUALITY

The quality data submitted with this application are satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY AND SAFETY

No clinical efficacy data are required for registration of Traditional Herbal Medicinal Products (THMP).

The Applicant has provided a bibliographic review which shows ample evidence for the use of Devil's Claw within the EU for a period exceeding 30 years.

A satisfactory review of the safety data has been provided.

The SPC, PIL and labelling are satisfactory.

RISK ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.

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STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Traditional Herbal Registration application on 9 January 2006
- 2 Following assessment of the application the MHRA requested further information relating to the dossier on 2 March 2006
- 3 The applicant responded to the MHRA's requests, providing further information on the dossier on 7 March 2006
- 4 Following assessment of the response the MHRA requested further information relating to the dossier on 20 October 2006
- 5 The applicant responded to the MHRA's requests, providing further information on the dossier 16 November 2006
- 6 Following assessment of the application the MHRA requested further information relating to the dossier on 7 December 2006
- 7 The applicant responded to the MHRA's requests, providing further information on the dossier on 8 December 2006
- 8 Following assessment of the response the MHRA requested further information relating to the dossier on 11 December 2006
- 9 The applicant responded to the MHRA's requests, providing further information on the dossier on 14 December 2006
- 10 Following assessment of the response the MHRA requested further information relating to the dossier on 21 December 2006
- 11 The applicant responded to the MHRA's requests, providing further information on the dossier on 22 December 2006
- 12 Following assessment of the response the MHRA requested further information relating to the dossier on 4 January 2007
- 13 The applicant responded to the MHRA's requests, providing further information on the dossier on 9 January 2007
- 14 A THR was granted on 26 January 2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flexiherb Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet contains 600 mg of extract (as dry extract aqueous) from Devil's Claw root (*Harpagophytum procumbens*) (equivalent to 900-1500 mg of Devil's Claw root).

Excipients: 1 film-coated tablet contains 170mg of lactose monohydrate and 20 mg of sucrose

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, oblong, smooth surface film coating without ruptures.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

A traditional herbal medicinal product used for the relief of backache, rheumatic or muscular pain, and general aches and pains in the muscles and joints, based on evidence of traditional use only.

4.2 Posology and method of administration

For oral short term use only. The patient should consult a doctor if symptoms worsen or do not improve after 8 weeks.

For adults and the elderly, take 1 tablet twice daily. Take one dose in the morning and one in the evening. The dose can be increased to 2 tablets twice daily if the patient does not obtain relief after 3-5 days. Tablets should be swallowed whole with a little liquid. The tablets should not be chewed.

This product is not indicated for use in patients less than 18 years old.

4.3 Contraindications

Active or previous gastric and/or duodenal ulcers.

Gallstones

Patients under 18 years of age.

Pregnancy

Lactation

4.4 Special warnings and precautions for use

Do not exceed the stated dose.

If the condition worsens, or if symptoms persist for more than eight weeks, or if adverse effects not mentioned in the package leaflet occur, consult a healthcare practitioner.

The dosing and safety of Devil's claw have not been studied thoroughly in children, and safety is not established.

This product contains sucrose.

1 film-coated tablet contains max. 20mg of sucrose or 0,031 carbohydrate units.

This product contains lactose.

1 film-coated tablet contains max. 170 mg lactose.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

Some studies in animals have shown effects on the heart, blood pressure and blood glucose. The clinical significance of these findings is unknown. In patients with heart disease/arrhythmias, diabetes, or blood pressure problems this product should be used with caution.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs that inhibit platelet aggregation, anticoagulants, non-steroidal anti-inflammatory agents (including aspirin and COX-2 inhibitors):

There is a theoretical risk that concomitant administration with Devil's claw may increase the risk of bleeding..

4.6 Pregnancy and lactation

The safety of the product during pregnancy and lactation has not been established. Therefore it should be avoided during pregnancy or lactation.

4.7 Effects on ability to drive and use machines

Some patients have experienced dizziness and somnolence while taking Devil's claw, which may affect the ability to drive and use machines.

4.8 Undesirable effects

Reports from clinical trials (18 studies with 2,219 patients treated with Devil's claw) show a cumulative incidence of adverse events of 4.4%. The most frequent adverse events (3.4%) were mild gastrointestinal complaints and included nausea and vomiting, constipation and diarrhoea, abdominal pain, flatulence, dyspepsia and heartburn. Mild allergic reactions were reported at an incidence of 0.31%. Other ADRs reported were tachycardia, cough, headaches, tinnitus, dizziness, somnolence and panic attacks. Their cumulative incidence was 0.59%.

4.9 Overdose

There are no data on human overdose with Devil's claw. Symptomatic and supportive measures should be taken as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The active constituents of Devil's claw have not been definitively established. However, the iridoid glycoside constituents, such as harpagoside, are considered to play an important role in its activity. It is thought that Devil's claw root does not produce the biochemical effects on arachidonic acid metabolism characteristic of anti-arthritic drugs such as the NSAIDs.

5.2 Pharmacokinetic properties

A pharmacokinetic study involving 3 healthy male volunteers measured plasma harpagoside concentrations after oral administration of Devil's claw extract (WS1531 containing 9% harpagoside) 600, 1200 and 1800 mg as film coated tablets. Maximal plasma concentrations were reached after 1.3-1.8 hours, and were 8.2 ng/mL and 27.8 ng/mL for doses of harpagoside of 108 and 162 mg, respectively (corresponding to 1200 and 1800 mg Devil's claw extract, respectively). Plasma half life has been reported between 3.7 and 6.4 hours.

5.3 Preclinical safety data

The preclinical toxicology data available are limited. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, powdered

Lactose monohydrate

Sodium Starch Glycolate (Type A)

Silica, colloidal anhydrous

Magnesium stearate

Sucrose

Titanium dioxide E 171

Hypromellose

Cellulose, microcrystalline

Stearic acid.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life is 3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Original packages contain 30, 40, 60 and 80 film-coated tablets

FlexiHerb film-coated tablets are packed in PVC/ PVDC- aluminium blisters and inserted into a carton.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

M H Pharma (UK) Ltd
t/a MedicHerb
PO Box 2835
Brewery Courtyard
Draymans Lane
Marlow
Buckinghamshire
SL7 2XG

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THR 23056/0001

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26/01/2007

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02/03/2007

PATIENT INFORMATION LEAFLET

Patient Information Leaflet

FlexiHerb[®] Film-coated tablets



Devil's Claw root extract 600mg

Please read this leaflet carefully before you start taking these tablets.
It contains some important information about FlexiHerb.

Keep this leaflet with the tablets.

You may want to read it again or show it to your doctor, pharmacist or healthcare practitioner.

What is in this leaflet

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1: What this product is and what it is used for

This product is a traditional herbal medicinal product containing Devil's Claw root. Each film-coated tablet of this product contains 600mg of a dry aqueous extract of Devil's Claw root (*Harpagophytum procumbens*) (equivalent to 900-1500mg of Devil's Claw root).

Flexiherb is a traditional herbal medicinal product used for the relief of backache, rheumatic or muscular pain, and general aches and pains in the muscles and joints. This usage is based on evidence of traditional use only.

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2: Before you take this product

DO NOT TAKE this product if you:

- have ever had or are suffering from a **stomach ulcer**
- have **gallstones**
- are **lactose-intolerant** (react badly to lactose or milk)
- are **pregnant or breastfeeding**
- are **allergic to any of the ingredients** (see section 6)
- are **under 18 years of age**

Tell your doctor before taking this product if you:

- have an **intolerance to some sugars** (see section 6)
- have **heart or blood pressure problems**
- have **diabetes**

If you are already taking warfarin, aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs, there is a theoretical risk that taking this product may increase the risk of bleeding.

3: How to take this product

Adults and the elderly

Take 1 tablet twice daily – the dose can be increased to 2 tablets twice daily if you do not obtain relief after 3-5 days.

Take one dose in the morning and one dose in the evening. You can take the tablets with or without food. Swallow the tablets whole with some water or other liquid. Do not chew the tablets.

Do not exceed the stated dose.

If you take too much of this product (overdose)

If you take more than the recommended dose, speak to a doctor, pharmacist or healthcare practitioner and take this leaflet with you.

If you forget to take this product

Continue to take your usual dose at the usual time, it does not matter if you have missed a dose.

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If you have any questions, or are unsure about anything, please ask your doctor, pharmacist or healthcare practitioner.

4: Side-effects

Like all medicines, this product can have side-effects. These are listed below.

Common side-effects (affecting approximately 1 in 20 people)	
<ul style="list-style-type: none">● nausea or feeling sick● indigestion● digestive upsets such as wind, bloating or diarrhoea	If these persist for more than a few days, or become troublesome, stop taking this product. These common side-effects are often only temporary.
Uncommon side-effects (affecting fewer than 1 in 300 people)	
<ul style="list-style-type: none">● mild allergic skin reactions itching and/or rash of the skin● cough, headache, tinnitus, tachycardia (increased heart beat), dizziness, drowsiness and panic attacks	Stop taking this product immediately if you experience any allergic skin reaction.
Other side-effects	
Devil's Claw may make you feel dizzy or sleepy. If you are affected do not drive or operate machines. Tell your doctor or pharmacist if you notice any other side-effect.	

5: After taking this product

You must speak to a healthcare practitioner if your symptoms worsen, if they do not improve after eight weeks, or if side-effects not mentioned in this leaflet occur.

Do not use your tablets after the expiry date. Return any out-of-date tablets to your pharmacist who will dispose of them for you. The expiry date is printed on the box and the blister pack.

Store the tablets in a cool dry place. Do not store the tablets in a place where the temperature goes above 25°C.

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Keep the tablets out of the reach and sight of children.

Keep your tablets in the blister pack until it is time to take them.

6: Product description

Each film-coated tablet contains 600mg of a dry aqueous extract of Devil's Claw root (*Harpagophytum procumbens*) (equivalent to 900-1500mg of Devil's Claw root)

This product also contains the following ingredients:

Powdered cellulose, lactose monohydrate, sodium starch glycolate (Type A), silica colloidal anhydrous, magnesium stearate, sucrose, titanium dioxide (E171), hypromellose, microcrystalline cellulose, stearic acid.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product. Each film-coated tablet contains 170mg of lactose and 20mg of sucrose.

Each pack contains 30, 40, 60 or 80 film-coated tablets.

Registration holder for this product

M H Pharma (UK) Ltd, t/a MedicHerb, PO Box 2835,
Brewery Courtyard, Draymans Lane,
Marlow, Bucks, SL7 2XG

Manufacturer of this product

Wiewelhove GmbH, Gildestrasse 39, 49477 Ibbenbüren, Germany

Traditional herbal registration number: THR 23056/0001

If you would like further information about this product, please contact:
M H Pharma (UK) Ltd, PO Box 2835, Marlow, Bucks SL7 2XG

Telephone: 01628 488487
Email: info@medicherb.co.uk

This leaflet was prepared in January 2007

For a large print, Braille or audio version of this leaflet, call 01628 488487

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LABELLING



FlexiHerb® 30 tablets



FlexiHerb®
film-coated tablets
Devil's Claw root extract 600mg

NEW



FlexiHerb® 30 tablets

A traditional herbal medicinal product used for the relief of

backache, rheumatic or muscular pain and general aches and pains in the muscles and joints

based on evidence of traditional use only



30 tablets

FlexiHerb®

MedicHerb

FlexiHerb®

A traditional herbal medicinal product used for the relief of backache, rheumatic or muscular pain, and general aches and pains in the muscles and joints, based on evidence of traditional use only.

Active ingredients: Each FlexiHerb® tablet contains 600mg of extract (as dry extract aqueous) from Devil's Claw root (*Harpagophytum procumbens*) (equivalent to 900-1500mg of Devil's Claw root).

This product contains lactose monohydrate and sucrose.

Dosage: For oral use. Adults and the elderly. For backache, muscular, joint or rheumatic aches and pains, take one tablet twice daily. The dose can be increased to 2 tablets twice daily, if you do not obtain relief after 3-5 days. The tablets should be swallowed whole with some water or other liquid.

Warning: Do not exceed the stated dose
Do not use if you: ● have ever had a stomach ulcer
● are under 18
● have gallstones
● are pregnant or breastfeeding
● are allergic to any of the ingredients

Devil's Claw may make you feel dizzy or sleepy. If you are affected, do not drive or operate machines.

Please read the enclosed information leaflet before taking these tablets. Keep out of sight and reach of children.

Do not store above 25°C
Store in original packaging

THR 3056/0001
 expiry date: see base

Manufactured in Germany
THR Soldey M H Pharma (UK) Ltd trading as MedicHerb)
PO Box 2895, Maidow, Bucks MK45 7 2JG
Telephone: 01628 488487 Email: info@medicherb.co.uk

Batch No: _____

Expiry date: _____



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