LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Läkemedelsverket 2015-03-20

Public Assessment Report
Scientific discussion

Curbisal, soft capsule

Serenoa repens (Bartram) Small, (saw palmetto) fructus, soft extract (9-11:1)

Asp no: 2008-0626

This module reflects the scientific discussion for the approval of Curbisal, soft capsule. The procedure was finalised in May 12, 2010. 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 Pharbio Medical International AB, Sweden, a marketing authorisation for the herbal medicinal product Curbisal, soft capsule. The product is available without prescription and can be bought from pharmacies and other outlets.

Curbisal has an extensive medicinal use in the EU for the treatment of minor complaints caused by benign prostatic hyperplasia (BPH), eg nocturia. The active ingredient is a soft extract from dried fruits of saw palmetto (sågpalmetto).

The Medical Products Agency has concluded that the active substance in Curbisal has a well-established medicinal use with a recognised efficacy and acceptable level of safety.

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 Curbisal could be granted a marketing authorisation as a herbal medicinal product.

I. INTRODUCTION

Pharbio Medical International AB, Sweden, has applied for a marketing authorisation for Curbisal, soft capsule. The application was submitted under Article 10a Well-established use application of the Directive 2001/83 EC, as amended.
The application is a national application for Sweden.

The active substance is *Serenoa repens* (saw palmetto) dried fruit, soft extract (9-11:1).
For approved indications, see the Summary of Product Characteristics (SmPC).

Curbisal, soft capsule, was first authorised as a natural remedy in 2006. As a consequence of the new legislation regarding (traditional) herbal medicinal products the product was reclassified as a herbal medicinal product in 2010.

II. QUALITY ASPECTS

II.1 Introduction

Curbisal is presented in the form of soft capsules containing 320 mg of the active substance *Serenoa repens* (saw palmetto) dried fruit, soft extract (DER= 9-11:1), corresponding to approximately 3.2g of dried fruit of *Serenoa repens*.

The excipients are: succinylated gelatin, glycerol (85%), purified water, glycerol, titanium dioxide [E171] and yellow iron oxide [E172]. These are all ingredients of the capsule shell.

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

The herbal substance, dried fruit of *Serenoa repens*, complies with the monograph “Saw palmetto fruit” in the European Pharmacopoeia and the general monographs for herbal drugs.

The plants are collected from the wild in the southeast of the United States. 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 ripe saw palmetto fruits are dried and extracted with ethanol 96%. After evaporation the resulting soft extract is homogenised and the lipophilic and hydrophilic phases are separated. Only the lipophilic phase is processed further.

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.

Control of the active substance (herbal preparation) *Serenoa repens* dried fruit, soft extract is based on the monograph “Saw palmetto extract” in the European Pharmacopoeia.

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.

II.3 Medicinal Product

Curbisal, soft capsules, are formulated using excipients described in the current European Pharmacopoeia. The gelatin in the capsule shell is derived from pigs. All raw materials used in the product are safe with regard to possible risk of TSE/BSE.

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 provided data support the shelf life claimed in the SPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

At the time of approval of the marketing authorisation for Curbisal, the safety and efficacy of *Serenoa repens fructus* had not been evaluated by the Committee on Herbal Medicinal Products (HMPC).

Assessment of the Curbisal application is based on evidence of well-established use as well as safety and efficacy data submitted by the applicant.

III.2 Pharmacology

The mechanism of therapeutic action cannot be considered clarified.

III.3 Pharmacokinetics

There are no pharmacokinetic studies concerning the saw palmetto extract in Curbisal soft capsule. The lack of pharmacokinetic data is acceptable since constituents responsible for the therapeutic effect of the extract are not entirely known, and thus pharmacokinetic studies are neither possible nor relevant.

III.4 Toxicology

No product specific data on genotoxicity for Curbisal has been presented. However, genotoxicity studies (Ames test) has been conducted for another saw palmetto extract, which is considered very similar to the Curbisal extract (DER= 9-12:1; extraction solvent: ethanol

94%). The study results did not indicate genotoxic properties. The information is considered satisfactory.

The inactive ingredients in Curbisal are well known and do not constitute any safety concern.

III.5 Ecotoxicity/environmental risk assessment

Curbisal is a herbal medicinal product. According to *Guideline on the environmental risk assessment of medicinal products for human use* (EMEA/CHMP/SW4447/00), herbal medicinal products are exempted from the obligation to present an environmental risk assessment due to the nature of their constituents.

III.6 Discussion on the non-clinical aspects

Based on the current knowledge and the available data on non-clinical safety (summarised above), Curbisal, soft capsule, can be recommended for approval.

IV. CLINICAL ASPECTS

IV.1 Introduction

At the time of approval of the marketing authorisation for Curbisal, the safety and efficacy of *Serenoa repens fructus* had not been evaluated by the Committee on Herbal Medicinal Products (HMPC).

Assessment of the Curbisal application is based on evidence of well-established use as well as safety and efficacy data submitted by the applicant.

IV.2 Pharmacokinetics

There are no pharmacokinetic studies concerning the saw palmetto extract in Curbisal soft capsule. The lack of pharmacokinetic data is acceptable since constituents responsible for the therapeutic effect of the extract are not entirely known, and thus pharmacokinetic studies are neither possible nor relevant.

IV.3 Pharmacodynamics

The mechanism of therapeutic action cannot be considered clarified.

IV.4 Clinical efficacy

Most experimental and clinical studies on the lipophilic extracts of the fruit of *Serenoa repens* have been performed using hexane extracts, whereas Curbisal contains an ethanol extract of saw palmetto. However, the applicant has provided information about the similarities between the present ethanolic and other lipophilic extracts (e.g. hexane). The ESCOP monograph is also cited in which the lipophilic extracts are not distinguished from each other. It is reasonable to accept that the clinical efficacy, which has been demonstrated for other lipophilic extracts, is valid also for ethanolic extracts.

A number of clinical studies on the use of lipophilic extracts of *Serenoa repens* have been performed, and metaanalyses are published. The conclusion is that extracts of *Serenoa repens* seems to be no more effective than placebo for the treatment of moderate to severe symptoms of BPH. However, nocturia is a symptom singled out as possibly positively affected by therapy with *Serenoa repens* preparations. Nocturia is a cumbersome symptom for patients. Thus, if a positive effect/risk relationship could be established for this symptom for products containing *Serenoa repens* extracts, Curbisal would be of help for patients affected.

IV.5 Clinical safety

A large number of patients have been treated with lipophilic extracts of *Serenoa repens* in controlled as well as open studies. Safety data concerning the exposure of 53 000 patient years to an ethanolic extract identical to that in Curbisal are available. Furthermore, sales data point to extensive exposure to *Serenoa repens* extracts in Germany.

The clinical safety documentation related to the use of products containing extracts of *Serenoa repens* (saw palmetto) indicates no signals of safety concern.

Patients are advised to contact a doctor before taking Curbisal to exclude serious diseases such as cancer in the prostate or urinary bladder.

If the symptoms worsen or persist for more than 6 months during the use of the medicinal product, a doctor should be consulted for a medical review of the condition.

Possible interaction with warfarin (increased INR) has been reported, and a causal relationship cannot be excluded. Therefore, a warning concerning concomitant use of anticoagulants is included in the SmPC.

Approval of Curbisal, soft capsule, as a herbal medicinal product with well-established use for the treatment of minor complaints caused by benign prostatic hyperplasia (BPH), eg nocturia, can be recommended with respect to clinical safety.

IV.6 Discussion on the clinical aspects

Based on the available data on clinical efficacy and clinical safety (summarised above), the benefit/risk ratio for Curbisal is considered positive, provided that the patients are advised to contact a doctor before taking Curbisal to exclude serious diseases such as cancer in the prostate or urinary bladder.

V. PRODUCT INFORMATION

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Curbisal, soft capsule, is recommended for approval.

VII. APPROVAL

Curbisal, soft capsule, was approved in the national procedure in 2010-05-12.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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