

Public Assessment Report

Scientific discussion

Solvenix, hard prolonged-release capsule

***Aesculus hippocastanum* L., semen, dry extract (4.5-5.5:1)**

Asp. No: 2008-0571

This module reflects the scientific discussion for the approval of Solvenix, hard prolonged-release capsule. The procedure was finalised at 3 September 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 product name “Venastat” and therefore this name is used throughout the document.

LAY SUMMARY

The Medical Products Agency (Läkemedelsverket, MPA) has granted Boehringer Ingelheim International GmbH, Germany, a marketing authorisation for the herbal medicinal product Venastat, hard prolonged-release capsule. The product is available without prescription and can be bought from pharmacies and other outlets.

Venastat, hard prolonged-release capsule, has an extensive medicinal use in the EU for the relief of symptoms caused by disturbances in the venous blood flow in the legs, so called chronic venous insufficiency, which is often accompanied by varicose veins, and which is characterised by swelling, a feeling of heaviness, pain, tiredness, itching, tension and cramps in the calf. To be used after chronic venous insufficiency has been established by a physician.

The active ingredient is dry extract of semen of *Aesculus hippocastanum* L.

The Medical Products Agency has concluded that the active substances in Venastat, hard prolonged-release capsule have 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 Venastat, hard prolonged-release capsule, could be granted a marketing authorisation as a herbal medicinal product.

I. INTRODUCTION

Boehringer Ingelheim International GmbH, Germany, has applied for a marketing authorisation for Venastat, hard prolonged-release 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 *Aesculus hippocastanum* L., semen, dry extract (4.5-5.5:1).

For approved indications, see the Summary of Product Characteristics (SmPC).

Venastat, hard prolonged-release capsule, was first authorised as a natural remedy in 2002. As a consequence of the new legislation regarding herbal medicinal products the product was reclassified as a herbal medicinal product in 2009.

II. QUALITY ASPECTS

II.1 Introduction

Venastat, hard prolonged-release capsule, is presented in the form of a hard prolonged-release capsule. One capsule contains 240 – 290 mg of the active substance; dry extract of *Aesculus hippocastanum* L., which corresponds to 50 mg of triterpene glycosides, calculated as anhydrous aescin. For the manufacturing of one capsule approximately 1.3 g of seeds of *Aesculus hippocastanum* L. is used.

The excipients are: dextrin, gelatin, copovidone, talc, purified water, ammonio methacrylate copolymer (Eudragit RS och Eudragit RL), titanium dioxide, triethyl citrate, sodium laurilsulfate, red iron oxide.

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

II.2 Drug Substance

The herbal substance *Aesculus hippocastanum* L., semen, is an in-house monograph based on the monograph in the German pharmacopoeia, DAB.

The plants used are collected from the wild in Hungary, Poland and Slovakia. 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 herbal drug is dried, milled and extracted using a maceration / percolation process with 50% ethanol. Extraction is followed by filtration and finally spray-drying after the addition of dextrin. The herbal preparation is a dry, standardised extract of horse chestnut seeds. The final aescin content is 16.7 %. DER is 4.5-5.5:1.

The manufacturing process has been adequately described and satisfactory specifications have been provided for starting materials and solvents.

The active substance 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

Venastat, hard prolonged-release capsule, is formulated using excipients described in the current European Pharmacopoeia, except for ammonio methacrylate copolymer (Eudragit RS och Eudragit RL) which is controlled according to U.S. Pharmacopeial Convention, and red iron oxide which is controlled according to the EEC Directive. 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.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC.

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 *Aesculus hippocastanum* L., semen, in 2009 and on *Aesculus hippocastanum* L., cortex, in 2012. In the monograph of the semen, it was concluded that the active substance in Venastat, hard prolonged-release capsule, *Aesculus hippocastanum* L., semen, dry extract has a well-established medicinal use with a recognised efficacy and acceptable level of safety in the Community in accordance with Directive 2001/83/EC.

The reader is referred to the Community monograph and the pertinent assessment report for details.

III.2 Pharmacology

The *Aesculus hippocastanum* L., semen, dry extract is a mixture of natural components. Triterpene glycosides such as aescin are believed to be important constituents in the dry extract of *Aesculus hippocastanum* L.

It is presently not known which compound or compounds are primarily responsible for the clinical effect.

III.3 Pharmacokinetics

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

Available preclinical data indicate low toxicity following oral administration of the dry extract of *Aesculus hippocastanum* L.

Concerning genotoxic potential of the product, the Applicant has performed a product/extract specific study using micronucleus assay. The test was performed with bone marrow cells of OF1 mice after single oral administration of the extract at 625 mg/kg body weight. No significant increase in the frequency of micro-nucleated polychromatic erythrocytes was observed.

The inactive ingredients in Venastat, hard prolonged-release capsule, do not constitute any safety concern.

III.5 Ecotoxicity/environmental risk assessment

Venastat, hard prolonged-release capsule, is a herbal medicinal product. According to *Guideline on the environmental risk assessment of medicinal products for human use* (EMA/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

Dry extract of *Aesculus hippocastanum* L. has been in medicinal use in the Community for a long period of time. The dry extract in Venastat, hard prolonged-release capsule, is recognised to have a well established medicinal use with an acceptable level of safety in the European Community.

No serious safety concerns have been identified.

IV. CLINICAL ASPECTS

IV.1 Introduction

The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has issued a Community monograph on *Aesculus hippocastanum* L., semen, in 2009 and on *Aesculus hippocastanum* L., cortex, in 2012. In the monograph of the semen, it was concluded that the active substance in Venastat, hard prolonged-release capsule, *Aesculus hippocastanum* L., semen, dry extract has a well-established medicinal use with a recognised efficacy and acceptable level of safety in the Community in accordance with Directive 2001/83/EC.

The reader is referred to the Community monograph and the pertinent assessment report for details.

IV.2 Pharmacokinetics

There are no studies concerning pharmacokinetics. 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 exact mechanism of action is not known, but preclinical and clinical pharmacological studies indicate that an effect on venous tone and capillary filtration rate is involved.

IV.4 Clinical efficacy

Based on a systematic review (meta analysis) of 17 clinical trials, it can be concluded that the dry extract of *Aesculus hippocastanum* L., semen (standardised on aescin) significantly reduces symptoms of chronic venous insufficiency, such as oedema, pain and itching compared to placebo.

IV.5 Clinical safety

The clinical safety documentation on Venastat, hard prolonged-release capsule, indicates no signals of safety concern. Approval of Venastat, hard prolonged-release capsule, as a herbal medicinal product with well-established use is therefore recommended with respect to clinical safety.

As no data on use in children are available, products containing *Aesculus hippocastanum* L., semen, *cannot* be recommended for use in children below the age of 18 years.

Due to lack of safety data, the use of products containing *Aesculus hippocastanum* L., semen, during pregnancy and lactation is not recommended.

There are no new signals of safety concern in the submitted product specific documentation relating to Venastat, hard prolonged-release capsule.

IV.6 Discussion on the clinical aspects

Venastat, hard prolonged-release capsule, is a herbal medicinal product available without prescription for the relief of symptoms caused by disturbances in the venous blood flow in the legs, so called chronic venous insufficiency, which is often accompanied by varicose veins, and which is characterised by swelling, a feeling of heaviness, pain, tiredness, itching, tension and cramps in the calf. To be used for treatment of medically confirmed chronic venous insufficiency.

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 adverse reactions reported during an extensive use of *Aesculus hippocastanum* L., semen, are no cause for safety concern. No new safety signals have been identified in the submitted product specific documentation relating to Venastat, hard prolonged-release capsule. The benefit/risk ratio is considered positive and Venastat, hard prolonged-release capsule, is recommended for approval.

VII. APPROVAL

Venastat, hard prolonged-release capsule, was approved in the national procedure on 2009-09-03.

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
Change of product name	5.4.3-2020-106010	Yes	2020-12-17	2021-02-01	Approval	No