HUNGARIAN NATIONAL CENTER FOR PUBLIC HEALTH AND PHARMACY

Public Assessment Report

Scientific discussion

VenoprotEP 500 mg film-coated tablets

Diosmin/Hesperidin 450/50 mg

HU/H/0612/001/MR

Date: 04.03.2026.

This module reflects the scientific discussion for the approval of VenoprotEP 500 mg film-coated tablets. The procedure was finalised at day 90 16.05.2019. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for VenoprotEP 500 mg film-coated tablets, from ExtractumPharma Co. Ltd.
The product is indicated in adults for:
treatment of chronic venous insufficiency of the lower extremities in case of the following functional symptoms:
- heavy legs and swelling
- pain
- nocturnal cramps of the lower limbs.
Symptomatic treatment of acute haemorrhoidal crisis.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(a) of Directive 2001/83/EC (well-established use).

Micronised diosmin-hesperidin, the active substance of the Applicant's product contains 90% diosmin (diosmetin-7-rhamnoglucoside) and 10 % other flavonoids (hesperidin, diosmetin, linarin, isorhoifolin, eriocitrin, isonaringin (narirutin), neohesperidin, naringenin, didymin, 6-iododiosmin and hesperetin) expressed as hesperidin (hesperitin-7- rhamnoglucoside). Diosmin differs molecularly from hesperidin by the presence of a double bond between two carbon atoms in diosmin's central carbon ring. Hence, diosmin can be manufactured by extracting hesperidin from citrus rinds, followed by conversion of hesperidin to diosmin (Diosmin Monograph Alternative Medicine Review 2004).

Diosmin was first isolated in 1925 and has been used therapeutically since 1960s. It was first marketed in Europe in 1971 and a new micronized formulation (smaller particle size) was introduced in 1986.

II. QUALITY ASPECTS

II.1 Introduction

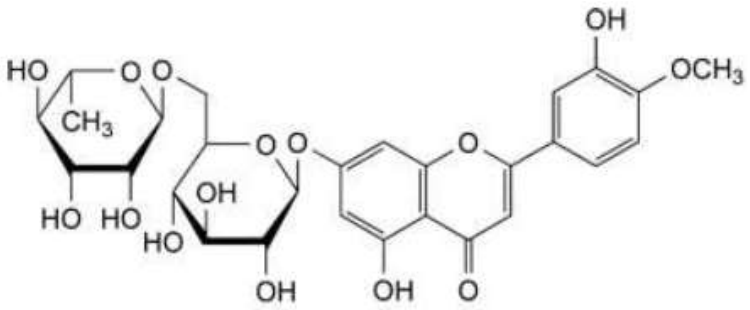
The chemical-pharmaceutical assessment report concerns the application of VenoprotEP 500 mg film-coated tablets via a mutual recognition procedure according to Article 10(a) of consolidated Directive 2001/83/EC (well-established use application).
The product has been developed by ExtractumPharma Ltd.
Objective of the development was to obtain immediate release tablets for oral administration containing micronized flavonoid fraction similarly to the already marketed product Detralex 500 mg film-coated tablets developed by Laboratoires Servier in which the active substance is defined as purified, micronized flavonoid fraction (which contains 450 mg diosmin and 50 mg other flavonoids expressed as hesperidin).

II.2 Drug Substance - Diosmin

Data on the quality and manufacture of the active substance diosmin were provided in the applicant's submission using the CEP procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: Diosmin
Chemical name: 7-[[6-O-(6-Deoxy-α-L-mannopyranosyl)-β-Dglucopyranosyl]oxy]-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one.

Structure:



The active substance is greyish-yellow or light yellow hygroscopic powder. It is practically insoluble in water, soluble in dimethyl sulfoxide, practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides. It does not exhibit polymorphism.
Micronization of the drug substance is performed by the drug substance manufacturer, to produce an active substance with particle size characteristics required by the drug product manufacturer. The brief flow-chart of the manufacturing process is provided.

The micronized drug substance is specified according to the requirements of the current Ph.Eur. monograph, additional specification has only been set for particle size distribution and microbial impurities. The specification is in accordance with the Ph.Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the micronized drug substance. According to the presented stability data the proposed re-test period of is acceptable with no special storage condition.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

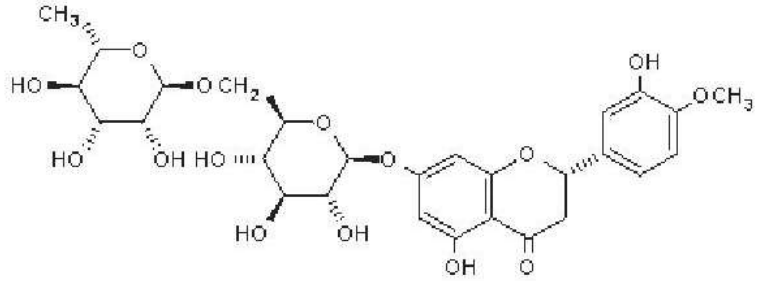
II.3 Drug Substance - Hesperidin

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure/ using the CEP procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

Data on the quality and manufacture of the active substance hesperidin were provided in the applicant's submission using the ASMF procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: Hesperidin
Chemical name: (S)-7-[[6-O-(6-Deoxy-α-L-manno-pyranosyl)-β-D-glucopyranosyl]oxy-2,3-dihydro-5-hydroxy-2-(3-hydroxy-4-methoxphenyl)-4H-1-benzopyran-4-one

Structure:



The active substance is a slightly brown to yellow powder, odorless. It is almost insoluble in water, soluble in dilute alkali. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.
Micronization of the drug substance is performed by the drug substance manufacturer, to produce an active substance with particle size characteristics required by the drug product manufacturer.

Evidence of the structure has been confirmed by the following methods spectroscopic: IR, ^{1}H-NMR, ^{13}C-NMR and MS spectrometry as well as XRDP, TGA and DSC. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Hesperidin is not official in the Ph.Eur. Specification limits are set according to the USP monograph on Hesperidin and relevant ICH guidelines. General Ph.Eur. methods are used for identification by IR, loss on drying, sulfated ash, heavy metals and microbiological quality.
The specification also includes the following in-house tests: solubility, identification, related substances, assay and particle size.

The presented specification is in accordance with the Ph.Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

No stability study has been performed with micronized hesperidin. Each active substance batch is controlled against the specification of drug substance prior to use by the drug product manufacturer.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.4 Medicinal Product

The aim of development was to formulate tablets containing well-known active substance, defined as 90% diosmin and 10% other flavonoids expressed as hesperidin, in micronized form.
A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

Orange-brown, oblong, film-coated tablets, with rounded edges and scored on both sides.
Length: ca. 18.2 ± 0.3 mm, Width: ca. 8.2 ± 0.3 mm, Thickness: 4.9 - 6.1 mm.

The excipients used for the core are gelatin, microcrystalline cellulose, maize starch, talc and magnesium stearate. The coating contains the following excipients: poly(vinil alcohol) – partially hydrolized, titanium dioxide (E171), macrogol, talc, yellow and red iron oxide (E172). All excipients used comply with their respective European Pharmacopoeia monograph, except yellow and red iron oxide (E172). They comply with USP. Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph.Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification.

The container closure system of the product is PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a **shelf-life of 4 years with no special storage conditions** is approved.
The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.5 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of the active substance are well known. The applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology studies have been presented and no such studies have been required for this application.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant and no such studies were required for this application.

III.4 Toxicology

No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The document presented by the applicant is adequate according to the EMA CHMP *Guideline on the Environmental Risk Assessment of medicinal products for human use* (EMA/CHMP/SWP/4447/00).

III.6 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of the active substance are well-known. No new nonclinical studies are needed. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacodynamics, pharmacokinetics, efficacy and safety of the active substance in the proposed indications, doses and dosing regimens are well known.

It is broadly acknowledged to be efficacious and to have an acceptable risk benefit profile.

In a well-established use application results of clinical trials are replaced by detailed references to published scientific literature.

IV.2 Pharmacokinetics

Absorption
After oral administration micronized diosmin and hesperidin are subjected to a rapid conversion in the intestinal lumen into diosmetin and hesperetin and then absorb as such. Maximum plasma concentrations of diosmetin and hesperetin are reached after 1-3 and 5 hours, respectively.

Distribution
In the systemic circulation both diosmetin and hesperetin are bound to plasma proteins primarily to human serum albumin.

Biotransformation
The drug is extensively metabolised as evidenced by the presence of various phenol acids in the urine.

Elimination
In man, following oral administration of 14C-labelled diosmin, the excretion is mainly faecal, a mean of 14% of the dose administered is excreted in the urine.
The elimination half-life is 11 hours.

IV.3 Pharmacodynamics

Mechanism of action
VenoprotEP 500 mg film-coated tablets reduces venous distensibility and decreases venous stasis. With respect to microcirculatory effects, it decreases capillary permeability and increases capillary resistance.

Pharmacodynamic effects
Dose-effect relationship
A statistically significant dose-effect relationship was established with respect to venous plethysmographic parameters: capacitance, distensibility and rate of emptying. The optimum dose-effect ratio was obtained with 2 tablets.

Venous tonic activity
Venous occlusion plethysmography demonstrated a decrease in the rate of emptying.

Microcirculatory activity
Double-blind controlled studies showed a statistically significant difference between placebo and the medicinal product. In patients presenting with signs of capillary fragility, micronized flavonoids increased capillary resistance, as measured by angiostereometry.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required for this type of application.
The applicant has provided an adequate literature review to describe the efficacy profile.
The data provided support the well-established efficacy of the active ingredient in the approved indications.

IV.5 Clinical safety

No new clinical safety studies have been presented and no such studies are required for this type of application.
The applicant has provided an adequate literature review to describe the safety profile.
The safety aspects are adequately reflected in the product information.

IV.6 Risk Management Plan

Product's name: VenoprotEP 500 mg film-coated tablets
Active substance: Diosmin/Hesperidin 450/50 mg
MAH: ExtractumPharma Co. Ltd.
Reference number: HU/H/0612/001/MR

1. Summary of Pharmacovigilance System

ExtractumPharma Co. Ltd. has submitted a signed Summary of the MAH Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

2. **Risk Management Plan** (version number: 0.2, dated on: 06.05.2019)

- **Summary of safety concerns**

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

- **Pharmacovigilance Plan**

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to VenoprotEP 500 mg film-coated tablets. No additional activities are proposed.

- **Risk Minimisation Measures**

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to VenoprotEP 500 mg film-coated tablets. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

3. **PSUR**

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application is based on a well-established use according to Article 10(a) of Directive 2001/83/EC as amended.
The quality of the product is adequate. The active substance diosmin has a well-established medicinal use with recognized efficacy and an acceptable level of safety.
Based on the review of the data on quality, efficacy and safety, the benefit-risk ratio for the product was considered positive.

Modul 6
Steps taken after the initial procedure with an influence on the Public Assessment Report

Procedure number	Type of modification [1]	Date of start of the procedure	Date of end of procedure	Approval/non approval
HU/H/0612/001/IB/001/G	A.2.b). for Nationally Authorised Products B.II.e).5.a).2. Change outside the range of the currently approved pack sizes Name change in PT	2019.11.22	2020.02.20	Approved
HU/H/0612/001/IA/002	B.III.1.a).2. Updated certificate from an already approved manufacturer	2020.02.27	2020.03.28	Positive
HU/H/0612/001/IB/004	A.2.b). for Nationally Authorised Products Name change in Belgium.	2020.07.03.	2020.08.02	Approved
HU/H/0612/001/IA/005	C.I.8.a). Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	2020.07.16	2020.08.15	Positive
HU/H/0612/001/IA/006	B.III.1.a).3. New certificate from a new manufacturer (replacement or addition)	2020.09.09	2020.10.09	Positive
HU/H/0612/001/IB/007	B.II.f).1.b).1. As packaged for sale (supported by real time data)	2020.11.03	2020.12.03	Approved
HU/H/0612/001/IA/009	B.II.b).4.a). Up to 10-fold compared to the originally approved batch size	2021.04.14	2021.05.14	Positive
HU/H/0612/001/IB/010/G	B.II.b).4.a). Up to 10-fold compared to the originally approved batch size	2021.04.14.	2021.05.14.	Approved
HU/H/0612/001/IB/011	B.I.b).2.e). Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	2022.07.12	2022.08.11	Approved
HU/H/0612/001/IA/012	A.1. Change in the name and/or address of the marketing authorisation holder	2023.01.16	2023.01.17	Positive
HU/H/0612/001/IA/015	A.4. Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites)	2023.08.24	2023.09.23	Positive
HU/H/0612/001/IA/013/G	B.I.a).1.z). Other variation B.I.a).3.a). Up to 10-fold increase compared to the originally approved batch size	2023.10.26	2023.11.25	Positive

HU/H/0612/001/IA/014/G	B.I.a).1.f). Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place	2023.08.15	2023.09.14	Positive
HU/H/0612/001/IA/016	B.III.1.a).3. New certificate from a new manufacturer (replacement or addition)	2024.02.05	2024.03.06	Positive
HU/H/0612/001/IA/017	A.4. Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites)	2024.06.17	2024.07.17	Positive
HU/H/0612/001/IA/019	B.II.b).3.a). Minor change in the manufacturing process	2024.12.18	2025.01.17	Positive