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Public Assessment Report

Name of the Product:

Zeflavon 500 mg film-coated tablets

(500 mg micronized flavonoids, as 450 mg diosmin and 50 mg other flavonoids expressed as hesperidin)

Procedure number: HU/H/0671/001/DC

Marketing authorisation holder: Zentiva, k.s.

Date: 20. 01. 2022.

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Zeflavon 500 mg film-coated tablets. The holder of the marketing authorisation is Zentiva, k.s.

The active substance is micronized flavonoids, as diosmin and other flavonoids expressed as hesperidin.

- Zeflavon 500 mg film-coated tablets: each film-coated tablet contains 500 mg micronized flavonoids, as 450 mg diosmin and 50 mg other flavonoids expressed as hesperidin.

The other ingredients are:

- tablet core: microcrystalline cellulose (Type 102); gelatin; maize starch; talc; magnesium stearate.
- tablet coat: partially hydrolysed poly(vinyl-alcohol); titanium dioxide (E171); macrogol 3350; talc; yellow iron oxide (E172); red iron oxide (E172).

The appearance of the tablets is:

– The 500 mg film-coated tablets are orange-brown, oblong film-coated tablets scored on both sides with length 18.2 ± 0.3 mm and width 8.2 ± 0.3 mm.

  The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The tablets are available in packs in blisters.

Zeflavon is a vasoprotector. It increases venous tone and the resistance of small blood vessels.

Zeflavon is indicated in adults:

- for the treatment of symptoms related to the chronic venous insufficiency of the lower extremities: heaviness of legs, swollen legs, pain, nocturnal leg cramps (pain that occur in the legs during the night).
- for the treatment of functional symptoms related to acute hemorrhoidal crisis, such as pain, bleeding and swelling in the anal region.

What patients need to know before using Zeflavon

Patients must not take Zeflavon if they

- are allergic to the active substance or any of the other ingredients of this medicine.

Warnings and precautions

Before taking Zeflavon, the doctor or pharmacist should be contacted.

Chronic venous disease:
In case of venous insufficiency, the treatment should be combined with a healthy lifestyle for getting the best results. Exposure to sun, heat, prolonged standing or becoming overweight should be avoided. Walking and wearing special (compression) socks improves circulation.

If patients' condition worsens during treatment, which can manifest as skin or vein inflammation, hardening of the tissue under the skin, severe pain, skin ulcers or atypical symptoms such as sudden swelling of one or both legs, the doctor should be talked to immediately.

Zeflavon will not help in reducing the swelling in your lower limbs if this is caused by heart, kidney or liver disease.

Acute hemorrhoidal disease:
In case of having an acute attack of haemorrhoids, Zeflavon may be taken only for a limited time of 7 days. If symptoms of acute hemorrhoidal crisis do not disappear within 7 days, the doctor should be talked to.

If the condition worsens during treatment, that is if patients notice increased bleeding from the rectum, blood in stools or are in doubt about bleeding haemorrhoids, they should consult the doctor.
Treatment with Zeflavon is not a substitute for the specific treatment of other anal disorders.

Children and adolescents

Zeflavon is not recommended for use in children and adolescents.

Other medicines and Zeflavon

The doctor or pharmacist should be told if patients are taking, have recently taken any other medicines or might take any other medicines.

No interactions with other medicines are presently known.

Pregnancy and breast-feeding

If patients are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, the doctor or pharmacist should be asked for advice before taking this medicine.

As a general precautionary measure, it is preferable to avoid the use of this medicine during pregnancy and breast-feeding. Due to lack of data concerning excretion into breast milk, taking this medicine is not recommended during breast-feeding.

Driving and using machines

This medicine has no or negligible influence on the ability to drive and use machines.

How to use Zeflavon

This medicine must always be taken exactly as described in this leaflet or the doctor or pharmacist has told. If patients are not sure the doctor or pharmacist should be checked with.

Chronic venous insufficiency:
The recommended dose for adults is two tablets a day for 2 months, one tablet at noon and one tablet in the evening with a meal. Treatment might be continued for further 2 months if justified by persistence of symptoms.

The doctor or pharmacist must be talked to if patients do not feel better or if they feel worse after 6 weeks if you are taking Zeflavon for the treatment of the symptoms of chronic venous disease. If there is a need to take Zeflavon further, the length of treatment will be decided by the doctor.

Acute haemorrhoidal crisis:
During the first 4 days of treatment, the recommended dose for adults is 3 tablets twice daily (6 tablets a day). During the following 3 days, the dose is 2 tablets twice daily (4 tablets a day).

These tablets should be taken with a meal.

In case of taking Zeflavon to treat symptoms of acute hemorroidal disease the doctor or pharmacist should be talked to if patients do not feel better or they feel worse after 7 days.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

What to do if more Zeflavon was taken that it should have been?

In the event of taking more tablets than it is advised, the doctor or pharmacist should be contacted.

There is limited experience with micronized flavonoids overdose. The adverse events in overdose could be diarrhoea, nausea, abdominal pain, pruritus, rash.

What to do if taking Zeflavon was forgotten?

No double dose to make up for a forgotten dose can be taken.

If any further questions have been raised on the use of this medicine, the doctor or pharmacist should be asked.

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

*Common***:** may affect up to 1 in 10 people
- nausea, vomiting, diarrhoea, dyspepsia.

Uncommon: may affect up to 1 in 100 people
- inflammation of the colon.

Rare: may affect up to 1 in 1,000 people
- headache, dizziness, malaise, rash, pruritus, urticaria.

Not known: frequency cannot be estimated from the available data
- isolated oedema of the face, lip or eyelids in association with allergic symptoms. Exceptionally Quincke's oedema may develop (the rapid evolving oedema of the face, lips, mouth, tongue or pharynx, which may be accompanied by breathing difficulties);
- abdominal pain.

How to store Zeflavon

This medicine does not require any special temperature storage conditions. It should be stored in the original package in order to protect from light and kept out of the sight and reach of children.

SCIENTIFIC DISCUSSION

This module reflects the scientific discussion for the approval of Zeflavon 500 mg film-coated tablets. The procedure was finalised at 08 February 2021. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member state, CMS: Bulgaria, Estonia, Italy, Lithuania, Latvia, Romania) concerned 500 mg micronized flavonoids, as 450 mg diosmin and 50 mg other flavonoids expressed as hesperidin

The application has been filed pursuant to Article 10(a) of Directive 2001/83/EC (well established use application) and therefore contained no new clinical or preclinical data, other than supporting literature where necessary.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Zeflavon 500 mg film-coated tablets from Zentiva, k.s.

Zeflavon 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 Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

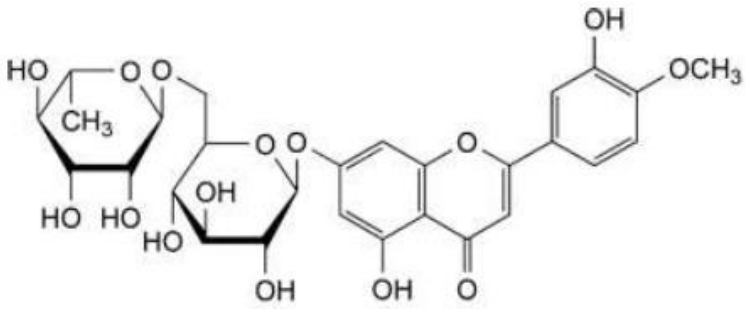
The chemical-pharmaceutical assessment report concerns the application of Zeflavon 500 mg film-coated tablets via a mutual recognition procedure according to Article 10(a) of consolidated Directive 2001/83/EC (well-established use application).

Objective of the development was to obtain immediate release tablets for oral administration containing micronized flavonoids 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 Sub-

stances 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.

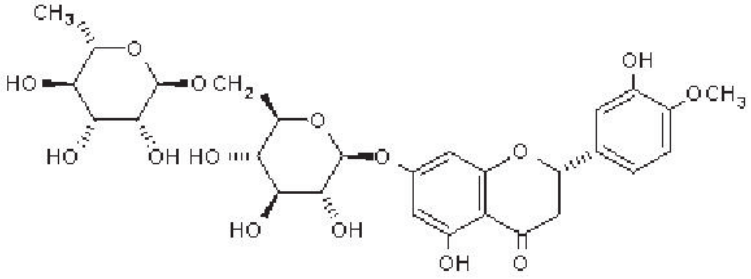
II.3 Drug Substance - Hesperidin

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 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, 1H-NMR, 13C-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

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

As the pharmacodynamic, pharmacokinetic and toxicological properties of diosmin-hesperidin are well known, no further non-clinical studies are required in support of this well-established use marketing authorisation and therefore no new non-clinical data was provided in this application.

The Applicant submitted a nonclinical overview based on a literature review of the pre-clinical pharmacology, pharmacokinetic and toxicology characteristics of diosmin-hesperidin which is considered adequate. No further studies are required.

III.2 Pharmacology

The active substance in Zeflavon 500 mg film-coated tablets is a glycosylated semisynthetic flavonoid (i.e. diosmetin-7-O-rutinoside) that belongs to the group of flavones.

The active substance is a well-known compound. No further new information was provided regarding the pharmacology of diosmin-hesperidin.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the Applicant.

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 CHMP Guideline on the ERA of medicinal products for human use (EMA/CHMP/SWP/4447/00 corr 2).

III.6 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of diosmin-hesperidin are well-known. 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 ingredient in the proposed indications, doses and dosing regimens are well known.

Diosmin-hesperidin has been widely marketed and used, and is well established in medicinal use. 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

Flavonoid glycosides have a relatively high molecular mass and hydrophilic nature, and thus they are poorly absorbed in the small intestine and pass unaltered to further parts of the alimentary tract, where intestinal bacteria such as *Eubacterium ramulus* are involved in their hydrolysis to aglycone and sugar. In the colon the heterocyclic aglycone structure is cleaved, leading to the formation of fluoroglucynole and phenolic acids (such as phenylpropionic and phenylacetic acids). Decomposition of flavonoids by bacteria also produces p-hydroxybenzoic acid, which is absorbed and used by leukocytes for the synthesis of coenzyme Q.

Orally administered diosmin-hesperidin is metabolised by intestinal bacterial flora to aglycone, i.e. to diosmetin, and is rapidly absorbed in this form from the alimentary tract.
Tmax for diosmetin is 1-2 hours.

Several studies demonstrated that micronized diosmin is better absorbed and has greater therapeutic efficacy than its non-micronized forms.

Distribution, metabolism, excretion
The metabolism of diosmin and diosmetin was monitored using HPLC and LC-MS. The levels of diosmin in plasma did not exceed 20 ng/ml, and only aglycone was detected, i.e. diosmetin with a mean retention time of 204 seconds. After one hour the mean plasma level of diosmetin was 400 ng/ml (Cmax 417 ±94.1 ng/ml).
Flavonoids are mainly metabolised in the liver, and most likely all types of flavonoid transformations are possible in this organ. These include methylation, hydroxylation and/or glycosylation. After a number of transformations in the liver, flavonoids, probably conjugated with proteins (the main albumin fraction) are transported to the peripheral circulation. It has been hypothesised that flavonoids, by binding with proteins, may become a structural part of lipoproteins, where, with vitamin E and other compounds, they can prevent lipoprotein oxidation. Further biological activity of flavonoids in plasma depends on the number of free ‘exposed’ function groups.

The half-life of diosmetin in plasma (T1/2) is from 26 to 43 hours (mean 31.5 h). The drug concentration gradually decreases, starting from the second hour after oral administration. However, traces of diosmin were still detected in plasma after 48 hours.
Diosmetin can be detected in plasma in unconjugated form or as the glucuronide or sulphate derivatives, due to the action of UDP-glucuronyltransferase enzymes and sulphotransferase.

Diosmin is metabolised to phenolic acids and their derivatives conjugated with glycine.

Diosmetin metabolites during the first 24 h of treatment are excreted in urine and faeces in comparable proportions, but mostly in faeces during the next 24 hours. The unabsorbed part of a diosmin and diosmetin dose and inactive diosmetin metabolites, mainly phenolic acids, are excreted in faeces.

IV.3 Pharmacodynamics

The clinical pharmacology of diosmin-hesperidin is well known. No novel pharmacodynamic data are supplied or required for this application.

Diosmin has a vasoprotective effect and increases venous tone (twice stronger than troxerutin) by prolonging the effect of noradrenalin in the venous wall, thus increasing the venous tone and sensitivity of myocytes to calcium ions. By improving blood return from the venous system diosmin reduces blood pressure and venous haemostasis in the limbs. It also increases capillary resistance.

Diosmin restores normal permeability in capillary vessels by inhibiting the release of pro-inflammatory mediators (histamine, prostaglandins and free radicals), reducing the activity of hyaluronidase and ceruloplasmin, and thus controlling inflammatory reactions, reducing oedema and protecting microcirculation.

Experimental studies on the use of diosmin in rats and dogs also demonstrated that diosmin increased lymphatic flow by up to 191% when compared to the control group, and the increase was dose-dependent. Experiments with 14C-labelled diosmin revealed that it is actively transported to the lymphatic system.

Flavonoids play an important protective role in pathological processes induced by oxidative stress, i.e. in cases of an imbalance between the uncontrolled oxidation and the activity of anti-oxidants in the body in favour of oxidation reactions. An antioxidant effect has been observed in different models, by scavenging active oxygen radicals, which protects the vascular cell membrane against aggression due to different irritants.

Diosmin inhibits the pathological activation, migration and adhesion of leukocytes to the vascular wall. It also increases lymphatic flow and lymph oncotic pressure. Diosmin, like other flavonoids, is considered a potent phosphodiesterase inhibitor, and therefore it increases the level of intracellular cAMP. This process decreases the levels of proinflammatory mediators, i.e. prostaglandin E2 (thus preventing vasodilation), prostaglandin F2α (preventing peripheral

hyperalgesia), thromboxane A2 and/or B2 (preventing platelet aggregation) and oxygen free radicals.
Diosmin significantly reduces the level of Endothelial Adhesive Molecules (EAM), and inhibits neutrophil activation, thus eliciting a protective effect on microcirculation.

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 of diosmin-hesperidin.
The data provided supports the well-established efficacy of the active ingredient in the approved indications.

IV.5 Clinical safety

No new safety data have been submitted and none are required for this type of application. The Applicant has provided an adequate literature review to describe the safety profile of diosmin-hesperidin.
The safety profile for diosmin-hesperidin is well-known and has been extensively described in the literature.
The safety aspects are adequately reflected in the product information.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The Applicant has submitted a signed Summary of the Applicant's 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.

IV.6.2 Risk Management Plan

Summary of safety concerns

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

As the active substance (diosmin and other flavonoids expressed in hesperidin) has been used for decades and its safety concerns are well-known, so there were no safety concerns applicable for this EU RMP based on the requirement to present only the important identified or potential

risks and missing information linked to further pharmacovigilance activities or additional risk minimization measures in the EU.

Pharmacovigilance Plan

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Zentiva's product containing diosmin and hesperidin.

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 Zentiva's product containing diosmin and hesperidin.

No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

The applications concern a well-established use product under Article 10(a) of Directive 2001/83/EC as amended.

The products are indicated for:
the 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.

Zeflavon 500 mg film-coated tablets is indicated in adults.

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Zeflavon 500 mg film-coated tablets. The applicant and the future holder of authorisation is Zentiva, k.s.

The application was submitted according to Article 10(a) of Directive 2001/83/EC (well established use application).

The product is indicated for:

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 acut haemorrhoidal crisis.

Zeflavon 500 mg film-coated tablets is indicated in adults.

The application contains an adequate review of published clinical data.
The active substance diosmin-hesperidin, has a well-established medicinal use with recognized efficacy and an acceptable level of safety in clinical medicine as outlined in the Clinical Overview. The compound is both effective and safe when used in accordance with recommendations published in the literature.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised. The therapeutic benefit/risk assessment is therefore positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Zeflavon 500 mg film-coated tablets from Zentiva, k.s.

V.2 Classification

Non Prescription

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
B.II.b).4. a) Up to 10-fold compared to the originally approved batch size	HU/H/0671/001/IA/001	no	25.06.2021	25.07.2021	approval	no
B.II.a).3.b). 1 Any minor adjustment of the quantitative composition of the finished product with respect to excipients B.II.b).3. a) Minor change in the manufacturing process B.II.b).5. z) Other variation B.II.d).1. z) Other variation	HU/H/0671/001/IB/002/G	no	04.10.2021	23.12.2021	approval	no