OGYÉI
National Institute of
Pharmacy and Nutrition

H-1051 Budapest, Zrínyi u. 3.
1372 P.O. Box:450.
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Public Assessment Report

Name of the Product:

Repaven

1000 mg film-coated tablets

(diosmin)

Procedure number: HU/H/0446/001/DC

Marketing authorisation holder: Egis Pharmaceuticals PLC

Date: 29 August 2017

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Repaven 1000 mg film-coated tablets (named Diosmin Hasco-Lek in Croatia, in this Public Assessment Report the name Repaven is used). The holder of the marketing authorisation is Egis Pharmaceuticals PLC.

The active substance is diosmin. Each film-coated tablet contains 1000 mg diosmin.

The other ingredients are: microcrystalline cellulose, povidone K 30, sodium starch glycolate (type A), magnesium stearate and the coating containing partially hydrolysed polyvinyl alcohol, macrogol 3350, macrogol 4000, talc, red iron oxide (E 172), yellow iron oxide (E 172) and titanium dioxide (E 171).

Repaven 1000 mg film-coated tablets (further on: Repaven) are pink, oval-shaped, biconvex, packed in PVC/PVDC foil blisters and aluminium foil and placed in a box with patient information leaflet.

The active substance of this medicine, diosmin improves flexibility and tension of vascular walls and protects blood vessels.

Repaven is used for the following therapeutic indications:
- symptomatic treatment of venous insufficiency of lower limbs:
    - leg pain and night crumps,
    - feeling of heavy legs;
- for treating symptoms of acute haemorrhoidal attacks.

Patients must talk to a doctor if not feeling better or if feeling worse.

What patients need to know before taking Repaven?

Those who are allergic to diosmin or any of the other ingredients of this medicine *should not take Repaven*.

Warnings and precautions

If haemorrhoidal symptoms do not subside or exacerbate during this treatment, a doctor must be consulted.

In case of haemorrhoidal symptoms, treatment with Repaven should be symptomatic and short-term.

Patients should discuss their doctor or pharmacist before taking Repaven.

Children and adolescents

The efficacy and safety in children and adolescents younger than 18 years have not been established.

Patients with renal and/or hepatic impairment

The efficacy and the safety of diosmin in patients with renal and/or hepatic impairment have not been established.

Other medicines and Repaven

Patients who taking, have recently taken or might take any other medicines should consult their doctor. No tests were conducted on drug interactions with Repaven.

Repaven with food and drink

This medicine should be taken during meals. The tablets may be swallowed directly with a glass of water, or dispersed in a half glass of water.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy: as the available medicinal data are insufficient, Repaven can be used by pregnant women only in the case of absolute necessity and only on the recommendation of the doctor.

Brest-feeding: as the rate of passage of the active substance of Repaven into human milk has not been precisely determined, this medicine should not be administered to breastfeeding women.

Driving and using machines

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

How to take Repaven?

The medicinal product should be taken orally. The tablets may be swallowed directly with a glass of water, or dispersed in a half glass of water.

The recommended dose is different according to the therapeutic indication.

For the *symptomatic treatment of venous insufficiency of lower limbs*:

- leg pain and night crumps,

- feeling of heavy legs

normally one film-coated tablet is recommended daily administered during a meal.

Only for the haemorrhoidal attacks: higher doses are recommended if haemorrhoidal symptoms exacerbate. One film-coated tablet 3 times daily for first 4 days, and for the next 3 days one film-coated tablet twice daily, in the morning and in the evening.

If haemorrhoidal symptoms do not subside or exacerbate during this treatment, a doctor must be consulted.

What to do if more Repaven has been taken than it should have been?

No symptoms of overdose are known, but a doctor or a pharmacist should be consulted.

What to do if taking Repaven has been forgotten?

Patients should not take a double dose to make up for a forgotten dose.

Possible side effects

Like all medicines, Repaven can cause side effects, although not everybody experiences them.

Rare cases of dermatological reactions (eczema, rash, pruritus, urticaria, pityriasis rosea) caused by hypersensitivity to diosmin were described.

Rare nervous system disorders (neuro vegetative symptoms) were also reported (insomnia, difficulty in falling asleep, dizziness and headache, anxiety, vertigo, irritability, tiredness, muscle cramps, palpitations or hypotension and drowsiness), which usually did not require discontinuation of diosmin and resolved shortly after the drug was discontinued.

Uncommon frequency (less than 2% of cases) has been reported to the gastrointestinal disorders (stomach ache, nausea, indigestion, vomiting, diarrhoea or other digestive tract disorders). Isolated cases of uterine bleeding and nosebleed have also been reported.

How to store Repaven?

It must be stored below 25°C in the original package in order to protect the film-coated tablets from moisture.

The medicine must be kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Repaven 1000 mg film-coated tablets. The procedure was finalised at 9 March 2017. 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 states, CMS: Bulgaria, Croatia and Romania) concerned the diosmin 1000 mg film-coated tablets (Repaven film-coated tablets, named Diosmin Hasco-Lek in Croatia).

The application has been filed pursuant to Article 10a of Directive 2001/83/EC (bibliographic submission and therefore contained no new clinical or preclinical data but literature review of the relevant bibliography. The active substance of the medicinal product, diosmin, has been in well-established medicinal use within the Community for at least 10 years, with recognized efficacy and an acceptable level of safety.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Repaven 1000 mg film-coated tablets of Egis Pharmaceuticals PLC.

The product is indicated for:
- symptomatic treatment of venous insufficiency of lower limbs:
  - leg pain and night crumps,
  - feeling of heavy legs;
- treatment of functional symptoms related to acute hemorrhoidal attacks.

It is indicated in adults.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

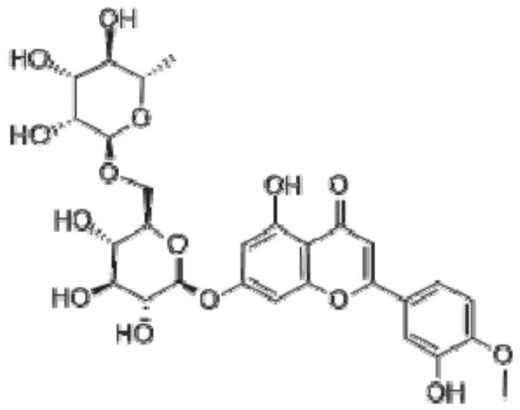
II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Repaven 1000 mg film-coated tablets via a decentralized procedure according to Article 10a of consolidated Directive 2001/83/EC (i.e. a well-established use application).

II.2 Drug substance

Data on the quality and manufacture of diosmin were provided in the applicant's submission using the European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (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-D-glucopyranosyl]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, practically insoluble in water and in ethanol (96 per cent). soluble in dimethyl sulfoxide. It dissolves in dilute solutions of alkali hydroxides.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specification has been set for residual solvents, microbiological purity and particle size distribution.

The Ph. Eur. specification includes the following tests for diosmin: identification, iodine content, heavy metals, water content, sulphated ash, related substances and assay.
The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Council on Harmonisation (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 European Medicines Agency (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.

A retest period and the packaging material have been specified on the CEP for diosmin.

Stability studies have been performed with the micronized drug substance. According to the presented stability data the claimed re-test period is acceptable in the same packaging material as mentioned on the CEP.

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

II.3 Medicinal product

The aim was to develop immediate release tablets for oral administration containing 1000 mg diosmin as active substance.

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 and composition was obtained: pink, oval-shaped, biconvex film-coated tablets with dimensions 17.0 x 9.8 mm

The excipients used in the finished product core were microcrystalline cellulose, povidon K-30, Sodium starch glycolate (Type A) and magnesium stearate. The coating (Opadry II Pink 85F24220) contains the following excipients: partially hydrolysed poly(vinyl) alcohol, titanium dioxide, talc, macrogol 3350, macrogol 4000, yellow and red iron oxide. All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. 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/PVDC//Al blisters and box. 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 2 years with the storage conditions “Store below 25°C in the original package in order to protect from moisture“ is approved.

The Summary of Product Characteristics, Patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Repaven 1000 mg film-coated tablets have been shown to meet the current regulatory requirements with regards to their 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 products.

From chemical-pharmaceutical points of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of diosmin 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 non-clinical pharmacology, pharmacokinetic and toxicology characteristics of diosmin which is considered adequate. No further studies are required.

III.2 Pharmacology

The active substance of Repaven 1000 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.

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 Ecotoxicology/environmental risk assessment

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 diosmin are well-known. No new non-clinical 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 ingredient in the proposed indications, doses and dosing regimens are well known.

Diosmin 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 is metabolised by intestinal bacterial flora to aglycone, i.e. to diosmetin, and is rapidly absorbed in this form from the alimentary tract. T_{max} 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.

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 (C_{max} 417 ± 94.1 ng/ml).

Flavonoids are mainly metabolised in the liver, and most likely all types of flavonoid transformation 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 ($T_{½}$) 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 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 proinflammatory 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 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 ^{14}C-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 antioxidants 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.

The data provided support 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.

The safety profile for diosmin 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 Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

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

Missing information	- Use in paediatric population - Use in pregnant women - Use in lactating women

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Repaven 1000 mg, film-coated tablets. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in the Summary of Product Characteristics, Package Leaflet and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to Repaven 1000 mg, film-coated tablets. No additional activities are proposed. For any further information on risk minimisation, 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

Well-established use (bibliographic) applications avoid the need for repetitive tests on humans. For these application the supportive literature data are pivotal.

The application concerns a well-established use product under Article 10a of Directive 2001/83/EC as amended.

The indication is the following:

Symptomatic treatment of venous insufficiency of lower limbs:
- leg pain and night crumps,
- feeling of heavy legs,

Treatment of functional symptoms related to acute hemorrhoidal attacks.

Repaven is indicated in adults.

The presented literature data support the application. Approval is recommended from the clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Repaven 1000 mg film-coated tablets. The applicant and the future holder of authorisation is Egis Pharmaceuticals PLC.

The product is indicated for adults for:

- symptomatic treatment of venous insufficiency of lower limbs:
  - leg pain and night crumps,
  - feeling of heavy legs;
- treatment of functional symptoms related to acute hemorrhoidal attacks.

The application was submitted according to Article 10a of Directive 2001/83/EC (well-established use or bibliographic application). Consequently, it contains an adequate review of published nonclinical and clinical data.

The active substance diosmin has a proven well-established medicinal use with recognized efficacy and an acceptable level of safety in clinical medicine as outlined in the Part IV. Clinical Aspects. 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 Diosmin 1000 mg film-coated tablets.

V.2 Classification

Prescription-only medicine.

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
IB A.2. Change of the (invented) product name in CMSs to DIH MAX 1000 mg film-coated tablets	HU/H/0336/001/IB/001	yes	26. 07. 2017		pending	no