# New Zealand Datasheet

## Name of Medicine

PAROVEN® capsules 250 mg
O-(β-hydroxyethyl)-rutosides

## Presentation

Opaque, greyish-yellow, hard gelatine capsules, for oral administration

## Uses

### Actions

Therapeutic Pharmacological Group: Vasoprotector (veins/capillaries)

The primary pharmacological effect of HR is a reduction of the capillary filtration rate of water and of microvascular permeability to proteins. This has been shown in a variety of experimental animal models and also in several clinical indications such as chronic venous insufficiency (CVI), idiopathic edema, liver cirrhosis, diabetic retinopathy. This effect on microvascular function may be explained by a reduction of inter-endothelial cell gaps, a modification of the inter-endothelial cell fibre matrix, and an increased adhesion of endothelial cells to the microvascular wall.

An inhibition of red cell aggregation and an increase in red cell deformability have also been demonstrated in man, which may explain the observed improvement in microvascular irrigation and in skin oxygen content. These pharmacological effects result in the reduction of oedema and related symptoms in chronic venous insufficiency and other indications characterised by an increased local microvascular permeability.

### Pharmacokinetics

The pharmacokinetics of O-(β-hydroxyethyl)-rutosides (HR) have been studied in the mouse, rate, rabbit, dog, rhesus monkey and in man. Increasing substitution of the hydroxyl groups of the parent rutin molecule, by hydroxyethyl groups of the parent rutin molecule, results in increased water solubility, an increased resistance of the molecule to bacterial degradation in the gut and also to reduction of protein binding. This weak and reversible protein binding of HR is globally around 30%. The detection of HR glycosides and their glucuronides in urine and bile (14-20% of an orally administered dose in the rate) is evidence of their absorption. There is a high rate of hepatic extraction, and enterohepatic circulation. Elimination is principally by the biliary route - about 65% of elimination - and the urinary route and is complete within 24-48 hours. HR does not pass the blood./brain barrier. Following oral or i.v. administration, transplacental passage of HR is minimal, only transient traces being found in the foetus of rats and mice. Similarly, traces only were found in the milk of lactating rats.

In man, after oral administration of 14C-HR, plasma peak concentrations are between 1-9 hours and detectable levels remain for 120 hours. The decline is bi-exponential. 3-6% of the administered radioactivity is excreted in the urine within 48 hours. The overall apparent half-life of elimination varies from 10-25 hours, but is relatively constant in the same subject. The biliary pathway of elimination of HR and its glucoronated metabolites has been confirmed in man.

### Indications

1. The treatment of the signs and symptoms of chronic venous insufficiency
    - heavy, painful and swollen legs and ankle oedema
    - paraesthesia

2. Post-thrombotic syndrome.
3. Varicose dermatitis.
4. Lymphoedema.
5. Symptomatic relief of haemorrhoids.
6. Prevention of skin and mucosal reactions to radio-therapy.

## Contraindications

Known hypersensitivity to any ingredient of the product.

## Adverse Reactions

Only isolated cases of mild adverse reactions have been reported (skin rashes, minor gastro-intestinal disturbances, headaches and flushes). They disappear rapidly on stopping treatment.

## Warnings and Precautions

Specific tolerability studies in patients with renal or hepatic insufficiency and in elderly patients have shown no signs of significant intolerance.

### Mutagenicity and Reproduction Toxicity Studies

All studies have shown that HR has no mutagenic potential.

Animal studies of reproductive toxicity have shown neither teratogenic potential nor other adverse effects of HR on the embryo and/or the foetus.

### Use in Pregnancy and Lactation

Paroven has been studied in clinical trials (1 controlled) in pregnant women, but not specifically during the first trimester.

Although no abnormalities have been observed in teratogenic studies or in humans, it is recommended, in accordance with general clinical practice, not to use O-(β-hydroxyethyl)-rutosides in the first three months of pregnancy. The traces found in the foetus and in breast milk (animal studies) are not considered to be of clinical relevance.

### Effects on Ability to Drive and Use Machines

None known.

## Interactions

No drug interactions have been reported. O-(β-hydroxyethyl)-rutosides has been shown not to interact with warfarin anticoagulants.

## Dosage and Administration

**Adults**

Initially, 1 capsule 3 or 4 times daily for 3 to 4 weeks. A clinical response to this level of dosage with PAROVEN may become apparent in 7 to 10 days and reach a maximum in 3 to 4 weeks.

In severe cases of lymphoedema the initial dosage may be increased up to 3 capsules 3 to 4 times daily for 3 to 4 weeks.

For maintenance therapy, a reduction in dosage to 1 capsule once or twice daily can be considered.

It is recommended that PAROVEN be taken with meals. The capsules must not be opened or chewed.

Clinical experience suggests that many patients will become symptom-free during the initial weeks of therapy. For these patients, treatment with PAROVEN may be stopped after about three months.

However, the recurrence of symptoms is an indication to recommence treatment with PAROVEN, 1 capsule 3 or 4 times daily, and continue at least until a remission is obtained. In these circumstances the level, and duration, of subsequent maintenance therapy should be carefully assessed against the individual case history.

Some patients will only remain symptom-free whilst treatment with PAROVEN is continued. Some adjustment to the recommended maintenance regimen (e.g. during summer/winter months) may be necessary.

**Children**
No information is available on the use of PAROVEN in children.

## Overdosage

No cases of overdosage with symptoms have been reported.

## Pharmaceutical Precautions

### Pharmaceutical Incompatibilities

None known to date.

### Shelf Life

5 years

## Special Precautions for Storage

Containers should be protected from moisture. Store below 30°C.

Medicines should be kept out of the reach of children.

## Medicine Classification

General Sale Medicine

## Package Quantities

Packs of 100 capsules

## Further Information

### Excipients

Polyethylene glycol 6000
Hard gelatine capsule
Yellow iron-oxide CI 77492 (E 172)
Titanium-dioxide CI 77891 (E 171)

## Name and Address

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## Date of Preparation

20 June 1999