

## New Zealand Datasheet

### Name of Medicine

PAROVEN<sup>®</sup> Forte

O-( $\beta$ -hydroxyethyl)-rutosides 500 mg

### Presentation

Paroven Forte, 500 mg tablets are greenish-yellow marbled, bi-convex circular tablets, for oral administration.

### Uses

#### Actions

Systemic vasoprotectors (bioflavonoide) / ATC Code: C05CA54

The pharmacodynamic effects of hydroxyethyl rutosides (HR) have been demonstrated in different in vitro and in vivo studies. At the cellular level the capability of HR to protect the vascular wall from the oxidative attack of activated blood cells and its affinity to the endothelium of capillaries and venules could be shown.

In studies in healthy individuals or in patients suffering from CVI the following pharmacodynamic effects of HR could be demonstrated:

- reduction of the capillary permeability
- restoration of the veno-arteriolar reflex
- increase of the venous refilling time
- increase of the transcutaneous oxygen tension.

All these effects are compatible with the primary effect of HR being on the microvascular endothelium, with a resultant diminution of oedema.

#### Pharmacokinetics

The standardised mixture of HR consists of mono-HR, di-HR, tri-HR, and tetra-HR, which differ in the number of their hydroxyethyl substituents.

After oral administration of <sup>14</sup>C-HR, peak plasma levels are detected after 2-9 hours. The plasma level declines progressively until 40 hours, after which the decline is very slow. This observation and the results obtained after i.v. administration, indicate that HR may be distributed to tissues (especially the endothelium of vessels), from which it is progressively and slowly released back into the circulation.

Plasma protein binding is 27-29%.

The main metabolic pathway of HR after oral administration is hepatic O-glucuronidation. The biliary pathway of elimination of HR and its glucuronated metabolites have been confirmed in man. Studies with <sup>14</sup>C-HR in laboratory animals demonstrated that in

addition to O-glucuronidation cleavage of the glycoside bond of HR, and fission of the central ring of mono-HR occur. HR and its metabolites are excreted by both the biliar and the renal route. Excretion via the renal pathway is complete after 48 hours. The mean terminal half-life of the main constituent of HR, the tri-HR, is 18.3 hours with a range of 13.5 to 25.7 hours.

In animal experiments it could be demonstrated that 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.

### **Indications**

Paroven Forte is indicated for the relief of oedema and related symptoms of chronic venous insufficiency (CVI) such as tired, heavy, swollen, painful legs, cramps, paraesthesia and restless legs.

As an adjuvant to elastic support (i.e. compression stockings) in CVI.

### **Dosage and Administration**

A series of studies, where doses between 500 mg and 2000 mg of HR daily have been used usually for periods of 1 to 3 months, showed that the optimal dose regimen is:

Initial dosage: Paroven Forte, 500 mg tablets: 1 tablet twice daily.

This dosage should be maintained until complete relief of symptoms and oedema. Symptomatic relief should usually be felt within 2 weeks.

Treatment may be continued as maintenance therapy for up to 3 months at the same dosage or at a minimum maintenance dosage of 500 HR daily, corresponding to 1 tablet Paroven Forte, 500 mg once daily

After complete relief of symptoms and oedema, treatment may also be stopped. On recurrence of symptoms, treatment can be resumed, at the same dosage or at a minimum maintenance dosage of 500 HR daily.

### **Contraindications**

Known hypersensitivity to any ingredient of the product.

### **Warnings and Precautions**

Patients who have oedemas of the lower limbs due to heart, kidney or liver disease should not use Paroven, because the effect of Paroven has not been shown in these indications.

### **Use in Pregnancy and Lactation**

In twenty-two different clinical trials a total of 1,431 pregnant women were treated with HR. The daily dose ranged in most studies between 600 and 1500 mg, with a range of 300 to 3,000 mg. The duration of treatment in most trials was between two weeks and four weeks, and up to five and six months in two trials. In these studies no foetal abnormalities were reported which could be attributed to the HR intake.

Nevertheless, according to generally accepted safety recommendations HR should not

be used during the first three months of pregnancy.

In animal studies traces of HR were found in the foetuses and in the milk of breast-feeding dams. These minor amounts of HR are of no clinical significance, however HR should not be used during breast feeding.

### **Effects on Ability to Drive or Use Machines**

None known.

### **Adverse Effects**

The type and frequency of adverse reactions reported in clinical trials were not significantly different from the ones observed in patients treated with placebo. These were mainly gastrointestinal disturbances (flatulence, diarrhea, gastric pain, gastric irritation), headache dizziness, tiredness, skin rashes, flushes and pruritus. They disappear rapidly on stopping treatment

### **Interactions**

No drug interactions have been reported. HR have been shown not to interact with warfarin anticoagulants.

The components of HR are derived from rutin and quercetin (present in trace quantities). Quercetin has been shown to inhibit human hepatic CYP3A and sulphotransferase in vitro but not in vivo. No inhibitory action of rutin has been shown on hepatic enzymes. It is therefore assumed that oral HR will not produce inhibitory effects nor interfere with the metabolism of other pharmacologically active substances.

### **Overdosage**

No cases of overdosage with symptoms have been reported.

### **Pharmaceutical Precautions**

Store below 30°C.

Medicines should be kept out of the reach of children.

### **Medicine Classification**

General Sale Medicine.

### **Package Quantities**

Cartons containing blisters of 60 tablets.

### **Further Information**

#### **Excipients**

Macrogol 6000, Magnesium stearate.

#### **Preclinical safety data**

HR has been studied for safety pharmacology single-dose toxicity, repeated-dose toxicity, genotoxicity, oncogenic potential, reproductive toxicity as well as local tolerance. The preclinical data reveal an almost complete absence of clinically relevant toxicological properties and favourable tolerability, indicating a very low toxicological risk and no special hazard for humans.

### Single-dose toxicity

In different animal models on acute toxicity testing, HR is well tolerated even at exceedingly high doses.

An LD<sub>50</sub> after oral administration could not be determined (> 5000 mg/kg b.w.). No signs of toxicity were observed even at 5000 mg/kg b.w.

The tolerance for intravenous administration in mice and rats was well above 1000 mg/kg b.w. Signs of toxicity could only be observed in the rat and consist of mild and non-specific symptoms like reduced activity, ataxia, and dyspnoea.

Intravenous application of 5000 mg/kg b.w. produced similar results in dogs.

### Repeated dose toxicity

In subacute toxicity studies over time periods of 90 days in rats and 30 to 90 days in dogs, no specific, HR-related toxic signs and symptoms were observed. No indication of specific organotoxic properties was found.

Studies on chronic toxicity over 52 weeks were conducted in mice and rats: In mice, at a dose of 5000 mg/kg b.w./day, no pathological changes attributable to HR were found. In rats, chronic administration up to 2700 mg/kg b.w./day resulted in slight, unspecific signs of toxicity, such as reduced food intake, decreased weight development and a slight decrease in haematocrit and haemoglobin at doses above 900 mg/kg b.w., which are considered to be a consequence of high-dose volumes. Even at the highest dose level, there was no unequivocal evidence of systemic toxicity. No organotoxic activities were observed.

### Reproductive toxicity

The results obtained in recent, ICH-conform trials on reproductive toxicity in rats and rabbits revealed no effects of HR on fertility, embryonic and foetal development, or the peri- and postnatal phase of the reproductive cycle.

There was no effect on the reproductive performance or behaviour in the progeny of HR-treated rats.

### Mutagenic potential

The mutagenic potential of HR was substantially investigated in *in-vitro* tests: Ames test, Specific Locus Mutation test, Chromosome Aberration test, Cell Transformation test and in an *in-vivo* assay (Micronucleus test).

There was no indication of mutagenic or cell-transforming properties of HR.

### Oncogenic/carcinogenic potential

Regular studies on oncogenic/carcinogenic properties of HR were not conducted.

However, studies on the genotoxic potential demonstrate no mutagenic and no cell-transforming effects of HR. Furthermore chronic treatment trials in rodents up to 52 weeks revealed no indication of hyperplastic, dysplastic, degenerative or neoplastic activities.

Local toxicity

According to the results of the maximization test in guinea pigs, HR displays no sensitising or irritating activities.

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