Renal excretion of parent compound is negligible (<0.5%). Urinary excretion of the glucuronide metabolite is low (5%), the metabolites are mostly (about 95%) excreted via the bile into the feces, with some evidence of enterohepatic recirculation.

**Pharmacokinetics in Elderly Subjects**
Plasma concentrations (determined as AUC) in elderly subjects (>65 years) were about 50% higher for tablet treatment and about 30% higher with intake of PERSANTIN 200 mg modified release than in young (<55 years) subjects. The difference with the modified release pellets is caused mainly by reduced clearance; absorption appears to be similar. A similar increase in plasma concentrations in elderly patients was observed in the ESPS2 study.

**Pharmacokinetics in Patients with Hepatic Impairment**
Patients with hepatic insufficiency show no change in plasma concentrations of dipyridamole, but an increase of (pharmacodynamically inactive) glucuronides. It is suggested to dose dipyridamole without restriction as long as there is no clinical evidence of liver failure.

**Pharmacokinetics in Patients with Renal Impairment**
Since renal excretion is very low (5%), no change in pharmacokinetics is to be expected in cases of renal insufficiency. In the ESPS2 trial, in patients with creatinine clearances ranging from about 15 ml/mm to >100 ml/mm, no changes were observed in the pharmacokinetics of dipyridamole or its glucuronide metabolite if data were corrected for differences in age.

**Indications**
As an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with mechanical prosthetic heart valves.

**Contraindications**
Hypersensitivity to any of the components of the product.
Side Effects
Adverse effects at therapeutic doses are usually mild and transient. Vomiting, diarrhea and symptoms such as dizziness, nausea, headache and myalgia have been observed. Such effects usually disappear on long-term use of PERSANTIN. As a result of its vasodilator properties, PERSANTIN may cause hypotension, hot flushes and tachycardia. Worsening of symptoms of coronary heart disease has been observed. Hypersensitivity reactions such as rash, urticaria, severe bronchospasm, and angio-edema have been reported. In very rare cases, increased bleeding during or after surgery has been observed. Isolated cases of thrombocytopenia have been reported in conjunction with treatment with PERSANTIN.

Dipyridamole has been shown to be incorporated into gallstones (see Warnings and Precautions).

Warnings and Precautions
Among other properties, dipyridamole acts as a vasodilator. If should be used with caution in patients with severe coronary artery disease, including unstable angina and recent myocardial infarction, left ventricular outflow obstruction or hemodynamic instability (e.g. decompensated heart failure). Patients treated with regular oral doses of PERSANTIN should not receive additional intravenous PERSANTIN.

In patients with myasthenia gravis, readjustment of therapy may be necessary after changes in dipyridamole dosage (see Drug Interactions).

A small number of cases have been reported in which unconjugated dipyridamole was shown to be incorporated into gallstones to a variable extent (up to 70% by dry weight of stone). These patients were all elderly, had evidence of ascending cholangitis and had been treated with oral dipyridamole for a number of years. There is no evidence that dipyridamole was the initiating factor in causing gallstones to form in these patients. It is possible that bacterial deglucuronidation of conjugated dipyridamole in bile may be the mechanism responsible for the presence of dipyridamole in gallstones.

Pregnancy and Lactation
There is inadequate evidence of safety in human pregnancy, but PERSANTIN has been used for many years without apparent ill-consequence. Preclinical studies have shown no hazard. Nevertheless, medicines should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh the possible risk to the fetus. PERSANTIN should only be used during lactation if considered essential by the physician.

Overdosage
Symptoms
Due to the low number of observations, experience with dipyridamole overdose is limited. Symptoms such as a warm feeling, flushes, sweating, restlessness, feeling of weakness, dizziness and angina can be expected. A drop in blood pressure and tachycardia might be observed.

Therapy
Symptomatic therapy is recommended. A gastric decontamination procedure should be considered. Administration of xanthine derivatives (e.g. aminophylline) may reverse the hemodynamic effects of dipyridamole overdose. Due to its wide distribution to tissues and its predominantly hepatic elimination, dipyridamole is not likely to be accessible to enhanced removal procedures.

Storage
Store below 30oC. Store in a safe place out of reach of children. Do not take the medicine after the expiry date printed on the pack.

Drug Interactions
Dipyridamole increases plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage should be considered.

When dipyridamole is used in combination with anticoagulants and acetylsalicylic acid, the statements on intolerance and risks for these preparations must be observed. Addition of dipyridamole to acetylsalicylic acid does not increase the incidence of bleeding
events. When dipyridamole was administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone. Dipyridamole may increase the hypotensive effect of drugs which reduce blood pressure and may counteract the anticholinesterase effect of cholinesterase inhibitors thereby potentially aggravating myasthenia gravis.

**Dosage and Administration**
A dosage range of 300-450 mg/day in divided doses is recommended. The maximum daily dose is 600 mg.
There is only limited information on the use of PERSANTIN in children.

**Packaging**
t: 25 rag, 75 mg (coated).
Composition
1 sugar-coated tablet contains 25 or 75 mg 2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimido-(5,4-d)-pyrimidine (= dipyridamole)

Excipients
25 mg - lactose, maize starch, aerosil 200, magnesium stearate, saccharose, t alc, acacia, titanium dioxide, polyethylene glycol 6000, beeswax white, carnauba wax, sunset yellow S.
75 mg - dibasic calcium phosphate, maize starch, aerosil 200, magnesium stearate, saccharose, t alc, acacia, titanium dioxide, polyethylene glycol 6000, beeswax white, carnauba wax, ironoxide red.

Pharmacological Properties
Dipyridamole inhibits the uptake of adenosine into erythrocytes, platelets and endothelial cells in vitro and in vivo; the inhibition amounts to 80% at its maximum and occurs dose-dependently at therapeutic concentrations (0.5-2 mcg/ml). Consequently, there is an increased concentration of adenosine locally to act on the platelet A2-receptor, stimulating platelet adenylate cyclase, thereby increasing platelet cAMP levels. Thus, platelet aggregation in response to various stimuli such as PAF, collagen and ADP is inhibited. Reduced platelet aggregation reduces platelet consumption towards normal levels. In addition, adenosine has a vasodilator effect and this is one of the mechanisms by which dipyridamole produces vasodilation.

Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. Whilst the inhibition of cAMP-PDE is weak, therapeutic levels inhibit cGMP-PDE, thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, identified as NO).

Dipyridamole also stimulates the biosynthesis and release of prostacyclin by the endothelium.

Dipyridamole reduces the thrombogenicity of subendothelial structures by increasing the concentration of the protective mediator 13-HODE (13-hydroxyoctadecadienic acid).

Metabolism of dipyridamole
Metabolism of dipyridamole occurs in the liver. Dipyridamole is metabolized by conjugation with glucuronic acid to form mainly a monoglucuronide and only small amounts of diglucuronide. In plasma about 80% of the total amount is parent compound, 20% of the total amount is monoglucuronide with oral administration.

Elimination of dipyridamole
Renal excretion of parent compound is negligible (<0.5%). Urinary excretion of the glucuronide metabolite is low (5%), the metabolites are mostly (about 95%) excreted via the bile into the faeces, with some evidence of entero-hepatic recirculation.

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**Symptoms**
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**Availability**
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