

New Zealand Datasheet

Name of Medicine

PERSANTIN[®]

Dipyridamole

Presentation

Tablet 25 mg: Round, orange, shiny, biconvex sugar-coated tablet.

Perlonget[®] (modified release capsule) 150 mg: Pink/white, opaque, hard gelatine capsule filled with yellow pellets.

Perlonget[®] (modified release capsule) 200 mg: Red/orange, hard gelatine capsule filled with yellow pellets.

Uses

Actions

Dipyridamole, the active ingredient of PERSANTIN, inhibits the uptake of adenosine into the 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 at 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).

Pharmacokinetics

For long-term treatment PERSANTIN modified release capsules, formulated as pellets have been developed. The pH dependent solubility of PERSANTIN which prevents dissolution in the lower parts of the gastrointestinal tract is overcome by means of a formula containing tartaric acid. Retardation of release is achieved by a diffusion membrane which is sprayed onto the pellets.

Absorption of dipyridamole

25 mg Tablets

After dosing with the sugar coated tablets there is a lag time of 10 to 15 minutes associated with disintegration of the tablet and gastric emptying. Thereafter the drug is rapidly absorbed and peak plasma concentrations are attained after 1 hour.

Geometric mean (range) peak plasma concentrations at steady state conditions with 75 mg t.d.s. were 1.86 µg/ml (1.23 - 3.27 µg/ml), and at trough were 0.13 µg/mL (0.06 - 0.26 µg/ml). With 75 mg q.i.d. corresponding peak concentrations were 1.54 µg/ml (0.975 - 2.17 µg/ml), trough concentrations were 0.269 µg/ml (0.168 - 0.547 µg/ml). With 100 mg q.i.d. corresponding peak concentrations were 2.36 µg/ml (1.13 - 3.81 µg/ml), trough concentrations were 0.432 µg/ml (0.186 - 1.38 µg/ml). The dose linearity of dipyridamole after single dose administration was demonstrated in the range from 25 to 150 mg,

Pharmacokinetic evaluations as well as experimental results in steady state conditions indicate that t.d.s. or q.d.s. dosage regimens are suitable. Treatment with dipyridamole tablets at steady state provides absolute bioavailability of approx. 60% and relative bioavailability of approx. 95% compared to an orally administered solution. This is partly due to a first-pass-effect from the liver which removes approx. 1/3 of the dose administered and partly to incomplete absorption.

Modified Release Capsules

Peak plasma concentrations are reached about 2 - 3 hours after administration. Mean peak concentrations at steady state conditions with 150 mg TWICE daily are 1.43 µg/ml (range 0.705 - 2.75 µg/ml), trough levels are 0.351 µg/ml (range 0.200 - 0.741 µg/ml). With a daily dose of 400 mg, the corresponding peak concentrations are 1.98 µg/ml (range 1.01 - 3.99 µg/ml), trough concentrations are 0.53 µg/ml (range 0.18 - 1.01 µg/ml). There is no clinically relevant effect of food on the pharmacokinetics of PERSANTIN 200 mg modified release capsules. The absolute bioavailability is about 70%. The dose linearity of dipyridamole after oral b.i.d. administration of the modified release capsules containing 150 and 200 mg was demonstrated.

As first pass removes approx. 1/3 of the dose administered, near to complete absorption of PERSANTIN modified release capsules can be assumed.

Various kinetic studies at steady state showed, that all pharmacokinetic parameters which are appropriate to characterise the pharmacokinetic properties of modified release preparations are either equivalent or somewhat improved with dipyridamole modified release capsules given b.i.d. compared to dipyridamole tablets administered t.d.s./q.d.s.: Bioavailability is slightly greater, peak concentrations are similar, trough concentrations are considerably higher and peak trough fluctuation is reduced.

Distribution of dipyridamole

Owing to its high lipophilicity, log P 3.92 (n-octanol/0.1n, NaOH), dipyridamole distributes to many organs. Non-clinical studies indicate that, dipyridamole is distributed preferentially to the liver, then to the lungs, kidneys, spleen and heart, it does not cross the blood-brain barrier to a significant extent and shows a very low placental transfer.

Non-clinical data have also shown that dipyridamole can be excreted in breast milk.

Protein binding of dipyridamole is about 97 - 99%, primarily it is bound to alpha 1-acid glycoprotein, and albumin.

Metabolism of dipyridamole

Metabolism of dipyridamole occurs in the liver. Dipyridamole is metabolised 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

Dominant half-lives ranging from 2.2 to 3 hours have been calculated after the administration of PERSANTIN. A prolonged terminal elimination half-life of approximately 15 h is observed. This terminal elimination phase is of relatively minor importance in that it represents a small proportion of the total AUC, as evidenced by the fact that steady-state is achieved within 2 days with both t.d.s. and q.d.s., regimens. There is no significant accumulation of the drug with repeated dosing. 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 bile into the faeces, with some evidence of entero-hepatic recirculation. Total clearance is approx. 250 ml/min and mean residence time is approx. 8 h (resulting from an intrinsic MRT of approx. 6.4 h and a mean time of absorption of 1.4 h).

Kinetics in elderly

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

Kinetics in patients with hepatic impairment

Patients with hepatic insufficiency show no change in plasma concentrations of dipyridamole, but increase of (pharmacodynamically inactive) glucuronides. It is suggested that dipyridamole may be dosed without restriction as long as there is no clinical evidence of liver failure.

Kinetics 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/min to >100ml/min, no changes were observed in the pharmacokinetics of dipyridamole or its glucuronide metabolite if data were corrected for differences in age.

Indications

Modified release capsules 150 mg are indicated:

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

Modified release capsules 200 mg are indicated:

- As an adjunct to oral anticoagulation for the prophylaxis of thromboembolism associated with mechanical prosthetic heart valves.
- In the secondary prevention of ischaemic stroke and transient ischaemic attacks, either alone, or in combination with acetylsalicylic acid.

Sugar coated tablet 25 mg are indicated:

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

Dosage and Administration

A dosage range of 300 - 450 mg / day in divided doses is recommended. In severe cases the total daily dose may be increased to 600mg. There is only limited information on the use of PERSANTIN in children.

For the secondary prevention of ischaemic stroke and transient ischaemic attacks, either alone, or in combination with acetylsalicylic acid, the recommended daily dose is 400 mg in divided doses. (usually one capsule in the morning and one in the evening) preferably with meals. The capsules should be swallowed whole without chewing.

PERSANTIN modified release capsules are not recommended for children.

Contraindications

Hypersensitivity to any of the components of the medicine.

PERSANTIN 25 mg sugar-coated tablets: In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to Warnings and Precautions) the use of the product is contraindicated.

Warnings and Precautions

Among other properties, PERSANTIN acts as a vasodilator. It should be used with caution in patients with severe coronary artery disease including unstable angina and recent myocardial infarction, left ventricular outflow obstruction or haemodynamic instability (e.g. decompensated

heart failure) patients treated with regular oral doses of PERSANTIN should not receive additional intravenous PERSANTIN.

Clinical experience suggests that patients being treated with oral dipyridamole who also require pharmacological stress testing with intravenous dipyridamole, should discontinue drugs containing oral dipyridamole for twenty-four hours prior to stress testing. Failure to do so may impair the sensitivity of the test.

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

PERSANTIN 25 mg sugar-coated tablets: One sugar-coated tablet contains 13 mg sucrose and 25 mg lactose monohydrate, resulting in 312 mg sucrose and 600 mg lactose monohydrate per maximum recommended daily dose for adults. Patients with the rare hereditary conditions of fructose intolerance or galactose intolerance, e. g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. PERSANTIN 25 mg sugar-coated tablets also contain the excipient sunset yellow (E 110), which may cause allergic reactions.

Fertility, Pregnancy and Lactation

Pregnancy

There is inadequate evidence of safety in human pregnancy, but PERSANTIN has been used for many years without apparent ill-consequence. Preclinical studies did not reveal any embryo-/fetotoxic effects during organogenesis in the peri - or post-natal phase. The NOELs for embryo/fetotoxicity were 40 mg/kg in rabbits, 125 mg/kg in mice and 1000 mg/kg in rats. Nevertheless, medicines should not be used in pregnancy, especially in the first trimester, unless the expected benefit is thought to outweigh the possible risk to the foetus. Dipyridamole is a medicine which has been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Lactation

PERSANTIN should only be used during lactation if considered essential by the physician.

Fertility

No studies on the effect on human fertility have been conducted with PERSANTIN. Non-clinical studies with dipyridamole did not indicate direct or indirect harmful effects with respect to the fertility index.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that they may experience undesirable effects such as dizziness during treatment with PERSANTIN. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

Adverse Effects

Adverse effects at therapeutic doses are usually mild and transient.

Gastrointestinal disorders

vomiting
nausea
diarrhoea

Nervous system disorders

dizziness
headache

Cardiac disorders

Angina pectoristachycardia.

Immune system disorders

Hypersensitivity
angio-oedema

Vascular disorders

hypotension
hot flush

Respiratory, thoracic and mediastinal disorders

bronchospasm

Skin and subcutaneous tissue disorders

rash
urticaria

Musculoskeletal, connective tissue and bone disorders

myalgia

Injury, poisoning and procedural complications

post procedural haemorrhage
operative haemorrhage

Blood and lymphatic system disorders

thrombocytopenia

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

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 or 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.

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 anginal complaints can be expected. A drop in blood pressure and tachycardia might be observed.

Treatment

Symptomatic therapy is recommended. A gastric decontamination procedure should be considered. Administration of xanthine derivatives (e.g. aminophylline) may reverse the haemodynamic 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.

Pharmaceutical Precautions

Store in a safe place out of reach of children.

Persantin 25 mg: store below 30°C

Persantin 150 mg and 200 mg: store below 25°C

Medicine Classification

Prescription Medicine

Package Quantities

Tablet, 25 mg, 84s

Perlonget 150 mg 60 capsule

200 mg, 60 capsules (not marketed)

Further Information

Clinical data for ischaemic stroke

In a randomised, placebo-controlled, double-blind study (European Stroke Prevention Study 2 - ESPS2) the efficacy of aspirin (ASA) and modified release dipyridamole (DP) in the secondary prevention of ischaemic stroke was examined. Patients with prior stroke or transient ischaemic attacks (TIA) were randomised to treatment with ASA alone (50 mg daily) or DP alone (400 mg daily), the two agents combined in a controlled formulation (Asasantin), or placebo. Primary endpoints were stroke, death, and stroke or death together. TIA and other vascular events were secondary endpoints. Patients were followed on treatment for 2 years.

Reduction in risk of stroke

Factorial analysis demonstrated a highly significant effect for ASA and for DP in reducing the risk of stroke ($p \leq 0.001$) and stroke or death combined ($p \leq 0.01$). In pairwise comparisons, stroke risk in comparison to placebo was reduced by 18% with ASA alone ($p = 0.013$); 16% with DP alone ($p = 0.039$) and 37% with combination therapy ($p = 0.001$). Risk of stroke or death was reduced by 13% with ASA alone ($p = 0.016$); 15% with DP alone ($p = 0.015$) and 24% with combination therapy ($p = 0.001$). The treatment had no statistically significant effect on death rate alone.

Reduction in risk of TIA

Factorial analysis also demonstrated a highly significant effect of ASA ($p < 0.001$) and DP ($p < 0.01$) for preventing TIA. The risk reduction for the combination was 36% ($p < 0.001$) in comparison with placebo.

Qualifying events as risk factors

Overall, the odds of suffering one or more TIAs were almost twice as high in patients with qualifying TIAs (306/1544, 19.8%) as in patients with qualifying strokes (555/4968, 11.2%). In the 4968 patients who had qualifying strokes and any follow-up TIA, ASA reduced the odds of having one or more TIA by 26% ($p = 0.001$, 95% C.I. 11% to 38%), whereas DP reduced the odds by only

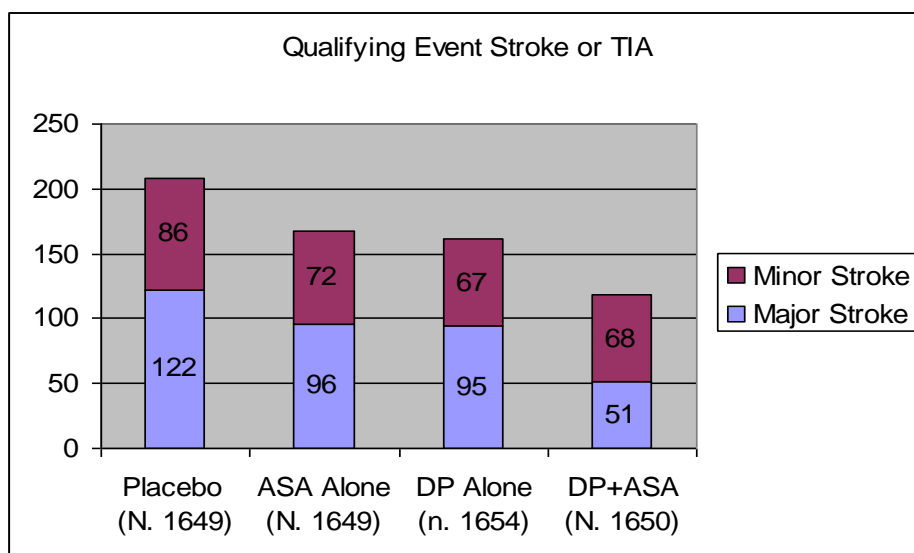
vs. 16.3%), this does not indicate increased risk, since the absolute number of fatal strokes was virtually the same (74 vs. 73). Similarly, the ASA group had a higher proportion of patients with minor stroke handicap than the no ASA group (39.5% vs. 34.0%), as well as a slightly higher proportion (but lower absolute number) of fatal strokes: 67 of 354 (18.9%) vs. 80 of 450 (17.8%), respectively.

Pairwise treatment comparisons also found no significant differences in the distribution of major/minor/fatal first-stroke handicap categories. A larger proportion of patients had minor stroke handicap on DP+ASA (45.3%) than on DP alone (32.7%), ASA alone (35.3%), or placebo (35.1%). The DP+ASA group had a higher proportion—but a lower absolute number—of fatal strokes (31 of 150, 20.7%) than either ASA alone (36 of 204, 17.6%) or placebo (37 of 245, 15.1%).

These findings show that patients are less likely to be moderately to severely disabled on DP+ASA than on placebo (48% odds reduction $p=0.020$, 95% C.I. 13% to 69%) after a non-fatal stroke. Note that the estimated 48% reduction in the odds of suffering major stroke handicap on DP+ASA vs. placebo represents a treatment benefit over and above the estimated 44% reduction in the odds of suffering a non-fatal stroke in the first place. ($p=0.021$, 95% C.I. 30% - 56%)

Thus DP+ASA appears to reduce the risk of major handicap after a non-fatal stroke, adding another dimension of clinical benefit to DP+ASA's demonstrated effectiveness in preventing non-fatal strokes.

Severity of Subsequent Stroke



Conclusion

The combination of ASA with DP effectively prevents recurrent stroke and recurrent TIA, both in patients with a recent ischaemic stroke and in patients with a recent TIA. It is also apparent that the severity of secondary stroke handicap is reduced by the combination of ASA and DP (odds reduction for major handicap 48%, 95% C.I. 13% to 69%, $p=0.020$) vs. placebo. The effect of the individual agents is additive, and once again results show that DP alone and aspirin alone reduce the odds of a major handicap (modified Rankin score 3 – 5) following a non-fatal stroke but these odds reductions are not statistically significant.

While the combination ASA with DP (ASASANTIN[®]) remains the first choice for secondary prevention of stroke and TIA, PERSANTIN[®] alone and aspirin alone are useful in those patients who cannot tolerate the one component of the combination (for example in patients who are aspirin intolerant).

PERSANTIN[®] is a registered trademark.

Excipients

Sugar-coated Tablets: lactose monohydrate, maize starch, starch soluble, silica colloidal anhydrous, magnesium stearate, sucrose, talc, acacia, titanium dioxide, polyethylene glycol 6000, beeswax white, carnauba wax, sunset yellow fcf.

Perlongets: tartaric acid, acacia, polyvidone 25, methacrylic acid methylmethacrylate copolymer (1:2), hypromellose phthalate, Hypromellose, triacetin, talc, dimethicone 350, stearic acid.

Gelatine Capsule 150 mg: - gelatin, iron oxide red (E172), titanium dioxide (E171).

Gelatine Capsule 200 mg: - iron oxide yellow, iron oxide red (E172), titanium dioxide (E171).

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