

New Zealand Data Sheet

1. PRODUCT NAME

Pytazen® SR modified release tablet, 150 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Pytazen SR Tablet contains dipyridamole 150 mg.

Excipient(s) with known effect

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Yellow capsule shaped tablets of 14 mm length, 6 mm width with a score on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Pytazen SR Tablets are indicated in prevention of post-operative thromboembolic complications associated with prosthetic heart valves; and in combination with aspirin, reduction in the rate of reinfarction in patients who have had a myocardial infarction.

4.2. Dose and method of administration

Dose

Adults

One tablet orally twice daily.

Paediatric population

Pytazen SR 150 mg Tablets are not recommended for children.

Method of Administration

The tablets must be swallowed whole and not crushed or chewed.

4.3. Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Among other properties, dipyridamole 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 dipyridamole should not receive additional intravenous dipyridamole.

Clinical experience suggests that patients being treated with oral dipyridamole who also require pharmacological stress testing with intravenous dipyridamole, should discontinue medicines 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 section 4.5).

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.

When dipyridamole is used in combination with anticoagulants or acetylsalicylic acid, the special precautions for these preparations should also be observed.

Should be used with caution in patients with coagulation disorders.

4.5. Interaction with other medicines and other forms of interaction

When dipyridamole is used in combination with anticoagulants or non-steroidal anti-inflammatory agents including 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.

Since dipyridamole inhibits platelet aggregation, combination with other platelet aggregation inhibitors, anticoagulants, other agents that can cause hypoprothrombinaemia or agents that can cause thrombocytopenia may be associated with an increased risk of haemorrhage. However, it has been shown that when dipyridamole was administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone.

Interactions and/or related problems may, however, arise if dipyridamole is considered for use in combination with heparin, cefamandole, cefoperazone, moxalactam, sodium valproate, pentoxifylline, tissue-type or recombinant plasminogen activator, streptokinase, urokinase or

cytotoxic agents.

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

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.

Pytazen Sustained Release tablets should not be taken at the same time as alcohol, as alcohol may increase the rate of release of dipyridamole from the sustained-release preparation.

4.6. Fertility, pregnancy and lactation

Pregnancy

Class B2 (Prescribing Medicines in Pregnancy 4th Edition). There is inadequate evidence of safety in human pregnancy, but dipyridamole 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.

Breast-feeding

Pytazen SR tablets 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 dipyridamole. Non-clinical studies with dipyridamole did not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7. Effects on ability to drive and use machines

Use of Pytazen SR tablets is presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery. However, if patients experience undesirable effects such as dizziness during treatment with PYTAZEN SR, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8. Undesirable effects

Adverse drug reactions (ADRs) at recommended doses are minimal and transient.

During initiation of therapy and as a result of its vasodilating properties, headache, dizziness, nausea, vomiting, diarrhoea, hypotension, hot flushes, tachycardia, syncope or weakness, and myalgia has occurred occasionally. Such effects usually disappear on long- term use.

Worsening of the symptoms of coronary heart disease such as angina and arrhythmias has occurred.

The frequencies of ADRs reported with dipyridamole based on clinical studies (where dipyridamole n = 1645) are summarised in table 1 below. With each frequency grouping ADRs are presented in order of decreasing seriousness.

The frequencies are defined as:

Very common $\geq 1/10$ ($\geq 10\%$)

Common $\geq 1/100 < 1/10$ ($\geq 1\%$ to $< 10\%$)

Uncommon $\geq 1/1,000 < 1 / 100$ ($\geq 0.1\%$ to $< 1\%$)

Rare $\geq 1/10,000 < 1/1,000$ ($\geq 0.01\%$ to $< 0.1\%$)

Very rare $< 1/10,000$ ($< 0.01\%$)

Table 1 Adverse drug reactions reported on clinical trial data

System Organ Class	Very Common $\geq 10\%$	Common $\geq 1\%$ to $< 10\%$	Rare $\geq 0.01\%$ to $< 0.1\%$
Nervous system Disorders	Headache, Dizziness		
Cardiac disorders		Angina Pectoris	
Gastrointestinal disorders	Diarrhoea, Nausea	Vomiting	
Skin and subcutaneous tissue disorders		Rash	
Musculoskeletal, connective tissue and bone disorders		Myalgia	

At high dosage levels, gastric irritation, emesis and abdominal cramping may occur.

Mild occasional gastric distress can be avoided by administration of tablets with a glass of milk. Dipyridamole has been shown to be incorporated into gallstones (see section 4.4).

When adverse reactions have been persistent or intolerable to the patient, withdrawal of the medication has been followed promptly by cessation of the undesirable symptoms.

When dipyridamole is used in combination with ASA for the secondary prevention of myocardial infarction, the only side effect clearly attributable to dipyridamole is headache. This symptom shows an increase of 5.5 % in the combination treated group over that occurring in a group of patients treated with ASA alone.

Other adverse reactions which occur during combination therapy are similar to those mentioned above together with the well documented side effects of ASA therapy, notably gastric distress and gastrointestinal bleeding. There may be an increase in the incidence of adverse reactions as the dose is increased.

Post marketing adverse effects

The ADRs identified during the ongoing market surveillance and for which a frequency could not be estimated are:

- Thrombocytopenia
- Hypersensitivity
- Angioedema
- Tachycardia
- Hypotension
- Hot flush
- Bronchospasm
- Urticaria
- Post procedural haemorrhage
- Operative haemorrhage

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions

<https://pophealth.my.site.com/carmreportnz/s/>

4.9. Overdose

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. Administration of xanthine derivatives (e.g. aminophylline) may reverse the haemodynamic effects of dipyridamole overdose. ECG monitoring is advised in such a situation. Due to its wide distribution to tissues and its predominantly hepatic elimination, dipyridamole is not likely to be accessible to enhanced

removal procedures.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin; ATC code: B01AC07

Dipyridamole has antithrombotic activity and is used in conditions where modification of platelet function may be beneficial.

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 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. It may also exert its effect by direct stimulation of the blood vessels to release prostacyclin and inhibit cellular uptake and metabolism of adenosine, giving an increased concentration at its platelet - vascular interface. In addition to these direct effects, dipyridamole has been shown to augment the platelet inhibiting action of aspirin through a pharmacokinetic interaction.

Following administration of dipyridamole, myocardial blood flow is increased in a dose related fashion with flows being 170 % or more above normal. Correlation studies of serum levels and the increase in coronary flow have shown that maximal increases are achieved at serum levels of 2 mcg/mL with the threshold being about 0.8 mcg/mL. The maximal response was achieved with single oral doses of 150 mg.

Dipyridamole does not produce a significant alteration of systemic blood pressure and heart rate, or of blood flow in the periphery at the therapeutically recommended doses.

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).

Platelet Function Studies

Dipyridamole has been shown to have a number of effects on platelet function and metabolism. *In vitro*, at high concentrations, dipyridamole inhibits platelet aggregation induced by ADP or collagen and, at lower concentrations, it potentiates the aggregation-inhibiting effects of adenosine and prostaglandin E. Dipyridamole also inhibits the uptake by platelets of adenosine, serotonin and glucose and increases platelet cyclic AMP levels. As determined by Hellem's method, when given to man, dipyridamole normalises increased platelet adhesiveness and tendency to aggregate.

Platelet Survival Time

In patients with artificial heart valves the platelet survival time has been shown to be reduced. A correlation between the incidence of thromboembolic phenomena and platelet survival time has also been demonstrated in these patients; the shorter the platelet survival, the higher the rate of thrombosis. Harker and Associates have shown that dipyridamole produces dose-related increases in the platelet survival time in patients with prosthetic valves, with 400mg/day normalising this parameter.

A dose of 3 g acetylsalicylic acid per day had little effect, while the combination of 100 mg dipyridamole per day plus 1 g ASA per day was as effective as 400 mg/day of dipyridamole alone.

Dipyridamole has been able to normalise a pathologically shortened platelet survival time (measured from the disappearance pattern of ⁵¹Cr-labelled platelets).

Thromboembolic Disease

Patients with artificial heart valves have an increased incidence of thromboembolic events. A 400 mg daily dose of dipyridamole has been shown to cause a significant reduction in the post-operative incidence of thromboembolic phenomena in patients who have had prosthetic heart valves inserted. This reduction has been demonstrated with both mitral and/or aortic valve replacement. In a controlled study, patients who received dipyridamole in a dose of 400 mg/day in combination with anticoagulants, the incidence of thromboembolic events was 1.3 % compared to 14.3 % in the control group treated with anticoagulants alone. There was no difference between the two groups with regard to haemorrhagic complications.

Coronary Artery Disease

The combined use of dipyridamole and acetylsalicylic acid (ASA) causes a significant reduction in the incidence of new fatal and non-fatal coronary events in patients with a previously documented myocardial infarction.

In a randomised, double-blind study, the effects of combined dipyridamole and ASA treatment were compared to ASA alone and to placebo in 2,026 patients who had suffered a myocardial infarction 8 weeks to 5 years previously.

Combined treatment with dipyridamole 75 mg and ASA 324 mg t.i.d., reduced the life-table rates for coronary incidence over a range of 37.0–66.7 % when compared to placebo in the 4–24 months period after starting treatment.

Similarly, for ASA alone, these reductions ranged from 29.1–52.4 % over the same period. The differences between dipyridamole-ASA treatment and placebo were statistically significant at each 4-monthly evaluation.

Differences between ASA alone and placebo were statistically significant only at 8 and 24 months. At the end of the follow-up, 41 months later, essentially no differences were found between ASA and dipyridamole-ASA treatment but both medicine treated groups showed 21–25 % lower coronary mortality and coronary incidence compared to placebo. This was no longer statistically significant.

Hospitalisation longer than 2 weeks for recurrent myocardial infarction was significantly reduced in both drug treatment groups compared to the placebo group.

The patient sub-group (447 or about 20 % of the total sample) entering the trial within 6 months after their last myocardial infarction showed the largest reduction in total and coronary mortality. However, the only statistically significant finding was a 63.6 % reduction in life table rates for coronary death in the dipyridamole-ASA group compared to placebo after 36 months of treatment.

5.2. Pharmacokinetic properties

Dipyridamole shows dose linearity for all doses used in therapy.

Dipyridamole is absorbed from the gastro-intestinal tract. The absolute bioavailability is about 70 %. As first pass removes approximately 1/3 of the dose administered, near to complete absorption of dipyridamole modified release preparations can be assumed. Following oral administration in man of 150 mg twice daily, peak plasma concentrations of approximately 1.5 mcg/mL (range 0.85–3.09 mcg/mL) are achieved about 2–3 hours after administration. Steady state is achieved within 2 days with twice daily dosing. There is no significant accumulation of the drug with repeated dosing and there is no clinically relevant effect of food on the pharmacokinetics of dipyridamole modified release preparations. The half-life ranges from 0.5–10 hours with a clearance of 2 mL/min/kg.

It is bound (range 91–99%) to acidic alpha-1-glycoprotein in plasma. The apparent volume of distribution of the central compartment (V_c) is about 5 L (similar to plasma volume). The apparent volume of distribution at steady state is about 100 L, reflecting distribution to various compartments. Total clearance is approximately 250 mL/min and mean residence time is about 11 hours (resulting from an intrinsic MRT of about 6.4 hour and a mean time of absorption of 4.5 hour).

Various kinetic studies at steady state have 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 preparations given twice daily compared to dipyridamole tablets administered three to four times daily. Bioavailability is slightly greater, peak concentrations are similar, trough concentrations are considerably higher and peak trough fluctuation is reduced.

Owing to its high lipophilicity, log P 3.92 (n-octanol/0.1 N, NaOH), dipyridamole distributes to many organs. In animals, dipyridamole is distributed preferentially to the liver, then to the lungs, kidneys, spleen and heart. The drug does not cross the blood-brain barrier to a significant extent.

Placental transfer of dipyridamole is very low. In one woman approximately 1/17th of the plasma concentration was detectable in breast milk.

Dipyridamole is metabolised in the liver and primarily excreted in the bile, with a small amount of parent compound being excreted in the urine (< 0.5 %). Urinary excretion of the glucuronide metabolite is also low (< 8 %). Enterohepatic recirculation has been shown, and this may delay excretion.

Kinetics in elderly

Plasma concentrations (determined as AUC) in elderly (> 65 years) were about 50 % higher after immediate release tablet treatment and about 30 % higher with dipyridamole modified release 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 increases in the pharmacodynamically inactive glucuronide. 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 (< 8 %), 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 > 100 mL/min, no changes were observed in the pharmacokinetics of dipyridamole or its glucuronide metabolite if data were corrected for differences in age.

5.3. Preclinical safety data

Mutagenicity

Mutagenicity assays (cytogenetic, micro-organism, dominant lethal and micronucleus tests) of dipyridamole did not demonstrate any mutagenic potential.

Carcinogenicity

Two year carcinogenicity studies of dipyridamole in mouse and rat in doses up to 75 mg/kg demonstrated no tumorigenic effect of the medicine.

Effect on Collateral Vessels of the Heart

The effect of chronic administration of dipyridamole on collateral vessels in the coronary circulation has been investigated in dogs, rabbits and pigs. In the presence of gradual constriction of one or two coronary vessels produced by ameroid rings, dipyridamole increases the number and diameter of intercoronary collateral vessels. This effect is associated with decreased mortality in the dipyridamole-treated animals compared with controls.

Chronic administration of dipyridamole to dogs influences intercoronary collateral vessels even in the absence of hypoxic stimulus. When dogs pretreated with dipyridamole are subjected to acute ligation of the main stem coronary artery, the subsequent flow across intercoronary vessels is greater than in control animals.

Studies on the effect of acute intravenous doses of dipyridamole on blood flow through experimentally produced infarcts have produced conflicting results. Some investigations have demonstrated an increase, while others have shown a decrease, or no change in blood flow into the ischaemic area.

Anti-Thrombotic Effects

It has been shown that dipyridamole reduced both the increased platelet consumption and thrombosis associated with the presence of foreign surfaces within the cardiovascular system of experimental animals.

Prophylactic administration of dipyridamole caused a reduction in the quantity of the thrombotic deposit seen on the surface of steel prostheses inserted in the right auricle of dogs. The administration of anticoagulants with dipyridamole increased this anti-thrombotic effect.

In another controlled study, Teflon vascular prostheses were implanted into the superior vena cava of dogs. Whereas the control animals had a relatively thick thrombotic deposit on the prostheses as early as 10 days following surgery, there were no thrombotic occlusions in the animals treated with 10 mg/ kg of dipyridamole i.v. and sacrificed 9 days and 6 months following surgery. Even prostheses removed 18 months after implantation showed only a thin layer of nonstenosing "neointima" without any deposition or accumulation of thrombotic material.

In pigs undergoing cardiopulmonary bypass, dipyridamole-treated animals (10 mg/kg) demonstrated increased perfusion of the microcirculation and a lesser fall in the platelet count, as compared to control animals.

Arteriovenous cannulation or infusion of homocystine in primates shorten platelet survival. Dipyridamole, at a dose of 100 mg/daily, or at a dose of 25 mg combined with 300 mg of acetylsalicylic acid, return the platelet survival time to normal. Acetylsalicylic acid given alone had no effect.

Acute toxicity

Oral LD50 (mg/kg)	
Mice	Greater than 10.0 g/kg
Rats	Greater than 10.0 g/kg

There were no deaths of mice or rats at all dose levels. The oral LD50 for mice and rats could only be estimated and was found to be greater than 10.0 g/kg of body weight. Mice at all dose levels appeared normal and healthy throughout the observation period, however, slight growth suppression of mice were observed at all dose levels. Little or no clinical symptoms were observed among rats at all dose levels. Rats were healthy and normal throughout the observation period and showed good weight gains.

Subacute Toxicity

Dipyridamole was administered i.v. to dogs for 6 days per week for one month. Groups of 4 dogs each were dosed at 1 mg/kg/day, 10 mg/kg/day and a control group. Emesis was noted in some animals. Haematology, biochemistry and pathology results were normal except for one dog which had haemorrhagic G.I. tract and thickened walls of the heart.

Rats were given a daily dipyridamole dose of 2.5 g/kg, 1.25 g/kg and 0.9 g/kg once a day with a gastric tube for one month. After oral administration the rats reduced spontaneous activity, calmed down and walked dragging the extremities. Erected hairs were noticed but no convulsion was seen. Four of 15 rats receiving 2.5 g/kg, two of 15 receiving 1.25 g/kg and no rats receiving 0.9 g/kg dipyridamole died within the first month.

Rats treated with a large dose of dipyridamole showed a marked increase of weight ratio of the liver to the body weight. Increase of weight ratio was also noticed in the adrenal gland and in the heart but not in the kidney and lung. There were no significant pathological changes in the preparations taken from the heart, liver and spleen.

In a few cases, congestion of the lung and oedema of hyaline degeneration of the kidney were observed.

Chronic Toxicity

A 6-month study in rats, 8 (4 male and 4 female) per group, administered 0 mg/kg, 30 mg/kg, 50 mg/kg, 70 mg/kg and 100 mg/kg 5 times weekly via stomach tube showed no negative pathology results, no weight differences and no deaths.

A 26-week study in dogs, 4 (2 male and 2 female) per group, administered oral doses of 0 mg/kg, 10 mg/kg/day, 20 mg/kg/day and 40 mg/kg/day, showed no deaths. Adverse effects noted in the 20 mg/kg/day and 40 mg/kg/day groups were thickened left ventricle wall increasing the relative heart weight. Other pathology was normal as was the biochemistry and haematology.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Acetone, Calcium phosphate (monobasic), Ethanol, Hypromellose, Isopropyl alcohol, Macrogol 4000, Magnesium stearate, Methacrylic acid copolymer, Purified talc, Quinoline yellow, Titanium dioxide.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 25°C. Protect from light and moisture.

6.5. Nature and contents of container

HDPE bottle, 60 tablets.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

25 June 1992

10.DATE OF REVISION OF THE TEXT

10 July 2024

Summary table of changes

Section Changed	Summary of new information
4.4	Added caution in coagulation disorders
4.5	Added alcohol related information
4.7	Added caution regarding dizziness
4.8	Added statement about worsening of coronary heart disease symptoms Added tabulated AE frequencies from clinical trials
4.9	Added new information – ECG monitoring
5.1	Mechanism of Action section updated