**PROFESSIONAL LEAFLET**

PERSANTIN® Ampoules 10 mg/2 ml Solution for Infusion

(dipyridamole)

**TRADE NAME OF MEDICINAL PRODUCT**
PERSANTIN Ampoules 10 mg / 2 ml Solution for Infusion

**QUALITATIVE AND QUANTITATIVE COMPOSITION**
Dipyridamole 5 mg/ml. Each 2 ml ampoule contains 10 mg dipyridamole.

**PHARMACEUTICAL FORM**
Solution for infusion.

**CLINICAL PARTICULARS**

**Therapeutic indications**

- **Adults:** As an alternative to exercise stress in thallium-201 myocardial imaging, particularly in patients unable to exercise or in those for whom exercise may be contraindicated.
- **Children:** As an alternative to exercise stress in myocardial perfusion imaging, particularly in children unable to exercise or in those for whom exercise may be contraindicated. More specifically, this may include children with Kawasaki disease complicated by coronary artery involvement, or those with congenitally abnormal coronary circulations.

**Posology and method of administration**

The dose of intravenous PERSANTIN as an adjunct to thallium myocardial perfusion imaging should be adjusted according to the weight of the patient. The recommended dose is 0.142 mg/kg/minute (0.567 mg/kg total) infused over 4 minutes.

Thallium-201 should be injected within 3-5 minutes following the 4-minute infusion of PERSANTIN.

**Contraindications**

- Hypersensitivity to any of the components of the product.
- Patients with dysrhythmias, second- or third degree atrioventricular block or with sick sinus syndrome should not receive intravenous PERSANTIN (unless they have a functioning pacemaker).
- Patients with baseline hypotension (systolic blood pressure < 90 mmHg), recent unexplained syncope (within 4 weeks) or with recent transient ischaemic attacks are not suitable candidates for dipyridamole testing.
- Patients with severe coronary artery disease, including unstable angina and recent myocardial infarction (within 4 weeks), left ventricular outflow obstruction or haemodynamic instability (e.g. decompensated heart failure).
- Patients with bronchial asthma or a tendency to bronchospasm.
- Patients with myasthenia gravis. (See Interactions.)
- Pregnancy and lactation.

**Special warnings and special precautions for use**

The potential clinical information to be gained through use of intravenous PERSANTIN as an adjunct in myocardial imaging must be weighed against the risk to the patient. Comparable reactions to exercise-induced stress may occur. Therefore dipyridamole-thallium scanning should be performed with continuous ECG monitoring of the patient.

When myocardial imaging is performed with intravenous PERSANTIN, parenteral aminophylline should be readily available for relieving adverse effects such as bronchospasm or chest pain. Vital signs should be monitored during and for 10 - 15 minutes following the intravenous infusion of PERSANTIN and an electrocardiographic tracing should be obtained using at least one chest lead.

Sedation may be necessary in young children.

Use with caution in young infants with immature hepatic metabolism.

Should severe chest pain or bronchospasm occur, parenteral aminophylline may be administered by slow intravenous injection; for adults, doses ranging from 75 mg to 100 mg aminophylline, repeated if necessary, are appropriate; for children, doses of 3-5 mg/kg aminophylline have been used.

In the case of severe hypotension, the patient should be placed in a supine position with the head tilted down if necessary, before administration of parenteral aminophylline. If aminophylline does not relieve chest pain symptoms within a few minutes, sublingual nitroglycerin may be administered. If chest pain continues despite use of aminophylline and nitroglycerin, the possibility of myocardial infarction should be considered.
If the clinical condition of a patient with an adverse effect permits a one minute delay in the administration of parenteral aminophylline, thallium-201 may be injected and allowed to circulate for one minute before the injection of aminophylline. This will allow initial thallium perfusion imaging to be performed before reversal of the pharmacologic effects of PERSANTIN on the coronary circulation.

Patients being treated with regular oral doses of PERSANTIN 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 drugs containing oral dipyridamole for twenty-four hours prior to stress testing.

Caution should be exercised in patients with known pre-existing first-degree heart block.

Interactions with other medicinal products and other forms of interaction
Xanthine derivatives (e.g., caffeine and theophylline) can potentially reduce the vasodilating effect of dipyridamole and should therefore be avoided 24 hours before myocardial imaging with PERSANTIN. For discontinuation of oral dipyridamole see section 4.4.

Dipyridamole increases plasma levels and cardiovascular effects of adenosine.

Dipyridamole may increase the hypotensive effect of drugs which reduce blood pressure.

Dipyridamole may counteract the anti-cholinesterase effect of cholinesterase inhibitors thereby potentially aggravating myasthenia gravis.

Fertility, pregnancy and lactation
Use of intravenous dipyridamole for cardiac stress testing in pregnancy and lactation is not recommended.

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 fertility (please refer to preclinical safety data).

Effect 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. If patients experience dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

Undesirable effects
When using as an adjunct to myocardial imaging, the following adverse events have been reported. Frequencies have been assigned based on two clinical trials of 73,806 and 3,911 patients.

Frequencies
- Very common ≥ 1/10
- Common ≥ 1/100 < 1/10
- Uncommon ≥ 1/1,000 < 1/100
- Rare ≥ 1/10,000 < 1/1,000
- Very rare < 1/10,000

Immune system disorders
Hypersensitivity rare
Anaphylactoid reaction very rare
Angioedema not known

Nervous system disorders
Headache very common
Dizziness very common
Paraesthesia common
Transient ischaemic attack rare
Convulsion very rare

Cardiac disorders
Chest pain/angina pectoris very common
Arrhythmia common
Tachycardia not known
Myocardial infarction uncommon
Cardiac arrest very rare
Ventricular fibrillation very rare
Sinus arrest not known
Atrioventricular block not known

Vascular disorders
Hypotension common
Hot flush common

Respiratory, thoracic and mediastinal disorders
Bronchospasm uncommon
Laryngospasm not known
Gastrointestinal disorders
Nausea common
Abdominal pain uncommon
Diarrhoea not known
Vomiting not known

Skin and subcutaneous tissue disorders
Urticaria not known
Rash not known

Musculoskeletal, connective tissue and bone disorders
Myalgia not known
Gastrointestinal disorders
Nausea common
Abdominal pain uncommon
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Vomiting not known

Further information

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Dipyridamole produces vasodilation. This effect and this is one of the mechanisms by which adenosine has a vasodilator action. Reduced platelet aggregation reduces stimuli such as PAF, collagen and ADP is inhibited. Consequently, there is an increased concentration of adenosine locally to act on the platelet A2-receptor, stimulating platelet adenylate cyclase, thereby augmenting the increase in cGMP released 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).

**Pharmacokinetic properties**

**Distribution**
Dipyridamole is metabolized by conjugation with glucuronic acid to form mainly a monoglucuronide and only small amounts of diglucuronide. After oral administration, dipyridamole is absorbed from the gut with peak plasma concentrations occurring in about 1 hour. Metabolism of dipyridamole occurs in the liver. Metabolism of dipyridamole produces two major metabolites: the monoglucuronide and the diglucuronide. Both metabolites are conjugated with glucuronic acid to form mainly a monoglucuronide and only small amounts of diglucuronide. After oral administration, dipyridamole is absorbed from the gut with peak plasma concentrations occurring in about 1 hour. Metabolism of dipyridamole occurs in the liver. Metabolism of dipyridamole is not likely to be accessible to enhanced removal procedures.

**Protein binding**
Protein binding of dipyridamole is about 97-99%, primarily it is bound to alpha 1-acid glycoprotein. It allows continued monitoring of the benefit-risk ratio of the medicinal product. It allows continued monitoring of the benefit-risk ratio of the medicinal product. It allows continued monitoring of the benefit-risk ratio of the medicinal product. It allows continued monitoring of the benefit-risk ratio of the medicinal product. It allows continued monitoring of the benefit-risk ratio of the medicinal product. It allows continued monitoring of the benefit-risk ratio of the medicinal product.

**Excretion**
Excretion in breast milk.

**Pharmacological properties**

**Pharmacodynamic 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 concentrations of 0.5–2 µg/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.
Elimination
After i.v. administration (60 mg/75 min) fitted by a 3-compartment model, a beta phase, with a half-life of about 40 min (dominant half-life) and a prolonged terminal elimination phase (λZ) with a half-life of about 15 hours are observed. According to this model, the beta phase represents the elimination of most of the administered drug and accounting for about 70% (together with the alpha phase) of the total AUC, whereas the terminal elimination phase (about 30% of the total AUC) probably represents the rediffusion of a smaller proportion of the administered dose from remotely accessible tissues of low capacity back into the central compartment.

Renal excretion of parent compound is negligible (< 0.5%). Urinary excretion of the glucuronide metabolite is low (< 8%), the metabolites are mostly (about 95%) excreted via the bile into the faeces, with some evidence of entero-hepatic recirculation. Total clearance is approximately 200 ml/min and mean residence time is 6.4 hours.

Elderly subjects
Plasma concentrations (determined as AUC) in elderly subjects (> 65 years) were about 30-50% higher with oral treatment than in young (< 55 years) subjects and the difference is caused mainly by reduced clearance; a slower decrease of plasma concentrations after i.v. treatment is to be expected.

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

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

Preclinical Safety Data
Dipyridamole has been extensively investigated in animal models and no clinically significant findings have been observed at doses equivalent to therapeutic doses in humans.

List of excipients
Tartaric acid
Macrogol 600
Hydrochloric acid
Water for injections

Incompatibilities
None stated.

Shelf Life
3 years.

Special precautions for storage
Keep container in the outer carton.

Nature and contents of container
Carton containing 5 x 2 ml colourless Type I glass ampoules.

Instructions for use, handling and disposal
None stated.

Marketing Authorisation Number
PL 0015/0119

Marketing Authorisation Holder
Boehringer Ingelheim Limited
Ellesfield Avenue
Bracknell
Berkshire
RG12 8YS, England

Manufacturer of the product
Boehringer Ingelheim España S.A.
Prat de la Riba, 50
08174 Sant Cugat del Vallés
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Legal Category
POM

Date of revision of the text
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In this leaflet:
1. What PERSANTIN Ampoules are and what they are used for
2. Before you receive PERSANTIN Ampoules
3. How PERSANTIN Ampoules will be given
4. Possible side effects
5. How to store PERSANTIN Ampoules
6. Further information

1. WHAT PERSANTIN AMPOULES ARE AND WHAT THEY ARE USED FOR

The name of your injection is PERSANTIN Ampoules 10 mg / 2 ml Solution for Infusion (called PERSANTIN Ampoules in this leaflet).
- It contains a medicine called dipyridamole. This belongs to a group of medicines called ‘coronary vasodilators’
- It works by opening up (dilating) the blood vessels in the heart
PERSANTIN Ampoules are used instead of exercise during scans to assess heart conditions.

2. BEFORE YOU RECEIVE PERSANTIN AMPOULES

You should not be given PERSANTIN Ampoules if:
- You are allergic (hypersensitive) to dipyridamole or any of the other ingredients of PERSANTIN Ampoules (listed in Section 6 below)
- You have heart problems such as a recent heart attack (within the last 4 weeks), angina (chest pain) at rest, irregular heart beat, heart block (this usually causes a slow heart beat), heart failure or a problem affecting the heart valves
- You have low blood pressure or have recently fainted (within the last 4 weeks) for no apparent reason
- You have had a stroke or something called a ‘transient ischaemic attack’ (a temporary stroke that lasts less than 24 hours)
- You have breathing problems such as asthma, shortness of breath or wheezing
- You have myasthenia gravis (a rare muscle problem)
- You are pregnant, likely to get pregnant or are breast-feeding

You should not receive this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before having PERSANTIN Ampoules.

Take special care with PERSANTIN Ampoules
Check with your doctor or pharmacist before having this medicine if:
- The person having the injection is a young infant whose liver is not fully grown

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because PERSANTIN Ampoules can affect the way some other medicines work. Also some other medicines can affect the way PERSANTIN Ampoules work.

In particular tell your doctor or pharmacist if you are taking any of the following medicines:
- Medicines used to treat high or low blood pressure
- Medicines that contain something called “xanthine derivatives” such as caffeine and theophylline. This also includes drinks such as tea, coffee and cola. If you have taken any of these, you need to wait at least 24 hours before having PERSANTIN Ampoules. This is because the caffeine can stop the injection working properly
- Medicines containing dipyridamole

Having PERSANTIN Ampoules with food and drink
You need to wait at least 24 hours before receiving PERSANTIN Ampoules if you have had a drink with caffeine in it such as tea, coffee or cola. This is because caffeine can stop the injection working properly.

Pregnancy and breast-feeding
You should not be given PERSANTIN Ampoules if you are pregnant, likely to get pregnant or are breast-feeding.

Driving and using machines
You may feel dizzy while receiving PERSANTIN Ampoules. If this happens do not drive or use any tools or machines.
3. HOW PERSANTIN AMPOULES WILL BE GIVEN

PERSANTIN Ampoules are usually given by a doctor or nurse. How much you are given depends on how much you weigh.

Receiving the injection
- PERSANTIN Ampoules are slowly injected into a vein over 4 minutes
- This process is often called having an infusion
- An injection of something called ‘thallium–201’ is then given within 3-5 minutes of the first injection

If you have more PERSANTIN Ampoules than you should
- It is unlikely that you will be given too much of this medicine. However, tell the doctor or nurse if you think that you have been given too much.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PERSANTIN Ampoules can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

The side effects described below have been experienced by people taking PERSANTIN Ampoules. They are listed as either very common, common, uncommon, rare, very rare or not known.

Very Common (affects more than 1 in 10 people)
- Headache
- Dizziness
- Chest pain

Common (affects less than 1 in 10 people but more than 1 in 100)
- Irregular heart beats
- Pins and needles (paraesthesia)
- Lower blood pressure than normal
- Hot flushes
- Feeling sick (nausea)

Uncommon (affects less than 1 in 100 people but more than 1 in 1,000 people)
- Heart attack
- Slower heart beat
- Difficulty in breathing or wheezing
- Gut (abdominal) pain

Rare (affects less than 1 in 1,000 people but more than 1 in 10,000 people)
- Hypersensitivity
- Stroke like symptoms that start suddenly but only last a short time
- Heart problems causing shortness of breath or ankles swelling

Very rare (affects less than 1 in 10,000 people)
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Stroke
- Fits (convulsions)
- Cardiac arrest
- Severe heart problem which causes abnormal and irregular heart beats (ventricular fibrillation)

5. HOW TO STORE PERSANTIN AMPOULES

- Keep out of the reach and sight of children
- PERSANTIN Ampoules should be kept in the outer carton
- Do not use the ampoules after the expiry date which is printed on the packaging

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What PERSANTIN Ampoules contain
- The active substance is dipyridamole. One 2 ml ampoule contains 10 mg dipyridamole
- The other ingredients in the injection are tartaric acid, macrogol 600, hydrochloric acid and water for injections

What PERSANTIN Ampoules look like and contents of the pack
- PERSANTIN Ampoules are clear glass vials containing a clear, yellow liquid. They are supplied in cartons of 5 ampoules.

Marketing Authorisation Holder and Manufacturer
- The Marketing Authorisation for PERSANTIN Ampoules is held by:
  - Boehringer Ingelheim Limited
  - Ellesfield Avenue
  - Bracknell
  - Berkshire
  - RG12 8YS
- and the ampoules are manufactured at:
  - Boehringer Ingelheim España S.A.
  - Prat de la Riba, 50
  - 08174 Sant Cugat del Vallés
  - Barcelona, Spain

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