SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

PERSANTIN Tablets 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dipyridamole 100 mg.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Coated Tablets.

Round, white, biconvex, shiny, sugar-coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

An adjunct to oral anti-coagulation for prophylaxis of thrombo-embolism associated with prosthetic heart valves.

4.2. Posology and method of administration

Adults:
300-600 mg daily in three or four doses.

Children:
PERSANTIN is not recommended for children.

PERSANTIN should usually be taken before meals.

4.3 Contraindications
Hypersensitivity to any of the components of the product.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to Special warnings and precautions for use) the use of the product is contraindicated.

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/or recent myocardial infarction, left ventricular outflow obstruction or haemodynamic instability (e.g. decompensated heart failure).

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.

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

PERSANTIN should be used with caution in patients with coagulation disorders.

A small number of cases have been reported in which unconjugated dipyridamole was shown to be incorporated into gallstones to a variable extent (upto 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 the bile may be the mechanism responsible for the presence of dipyridamole in gallstones.

One sugar coated tablet contains 49 mg sucrose, resulting in 294 mg sucrose per maximum recommended daily dose for adults. Patients with the rare hereditary conditions of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Dipyridamole increases plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage should be considered if use with dipyridamole is unavoidable.

There is evidence that the effects of aspirin and dipyridamole on platelet behaviour are additive.

The administration of antacids may reduce the efficacy of PERSANTIN. It is possible that PERSANTIN may enhance the effects of oral anti-coagulants.

When dipyridamole is used in combination with any substances impacting coagulation such as anticoagulants and antiplatelets, the safety profile for these medications 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.

4.6 **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. Animal studies have shown no hazard. Medicines should not be used in pregnancy, especially the first trimester unless the expected benefit is thought to outweigh the possible risk to the foetus (please refer to section 5.3).

**Lactation**
Dipyridamole is excreted in breast milk at levels approximately 6% of the plasma concentration. Therefore 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 fertility (please refer to section 5.3).

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

4.8 **Undesirable effects**

Adverse effects at therapeutic doses are usually mild and transient

The following side effects have been reported, frequencies have been assigned based on a clinical trial (ESPS-2) in which 1654 patients received dipyridamole alone.

**Frequencies**

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>$\geq 1/10$</td>
</tr>
<tr>
<td>Common</td>
<td>$1/100 &lt; 1/10$</td>
</tr>
<tr>
<td>Uncommon</td>
<td>$1/1,000 &lt; 1/100$</td>
</tr>
<tr>
<td>Rare</td>
<td>$1/10,000 &lt; 1/1,000$</td>
</tr>
<tr>
<td>Very rare</td>
<td>$&lt; 1/10,000$</td>
</tr>
</tbody>
</table>
Blood and lymphatic system disorders
Thrombocytopenia not known

Immune system disorders
Hypersensitivity not known
Angioedema not known

Nervous system disorders
Headache very common
Dizziness very common

Cardiac disorders
angina pectoris common
tachycardia not known

Vascular disorders
Hypotension not known
Hot flush not known

Respiratory, thoracic and mediastinal disorders
Bronchospasm not known

Gastrointestinal disorders
Diarrhoea very common
Nausea very common
Vomiting common

Skin and subcutaneous tissue disorders
Rash common
Urticaria not known

Musculoskeletal, connective tissue and bone disorders
Myalgia common

Injury, poisoning and procedural complications
post procedural haemorrhage not known
operative haemorrhage not known

Dipyridamole has been shown to be incorporated into gallstones (please refer to section 4.4 Special warnings and precautions for use).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

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.

**Therapy**
Symptomatic therapy is recommended. 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.

5  **PHARMACOLOGICAL PROPERTIES**

5.1  **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 therapeutic concentrations (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.

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)

5.2  **Pharmacokinetic properties**

After dosing with the sugar-coated tablets there is a lag time of 10 - 15 min 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.

Distribution
Owing to its high lipophilicity, log P 3.92 (n-octanol/0.1 N, 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
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
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 the 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).

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 capsules than in young (<55 years) subjects.
The difference 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.

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.
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.

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core:
- Calcium hydrogen phosphate, anhydrous
- Maize starch, dried
- Modified starch (corn starch, oxidised)
- Colloidal anhydrous silica
- Magnesium stearate

Coating:
- Sucrose
- Talc
- Acacia
- Titanium dioxide, E171
- Macrogol 6000
- Wax, bleached
- Carnauba Wax

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Do not store above 30°C. Protect from light.
6.5. Nature and contents of container

PVC/PVDC/Aluminium Blisters
Pack sizes of 84, 100 or 112 sugar coated tablets.
Not all pack sizes may be marketed

6.6. Instructions for use, handling and disposal

None.

7 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Limited
Ellesfield Avenue
Bracknell
Berkshire
RG12 8YS
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00015/5016R

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/05/2007

10 DATE OF REVISION OF THE TEXT

21/10/2016