

ASASANTIN[®] SR

SUSTAINED-RELEASE CAPSULES

NAME OF THE MEDICINE

Active ingredients: dipyridamole
aspirin

Dipyridamole

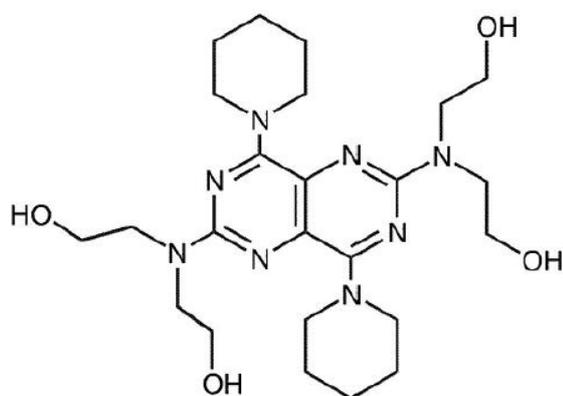
Chemical name: 2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimido[5,4-d]pyrimidine

Molecular formula: C₂₄H₄₀N₈O₄

CAS number: 58-32-2

Molecular weight: 504.6

Structural formula:



Aspirin

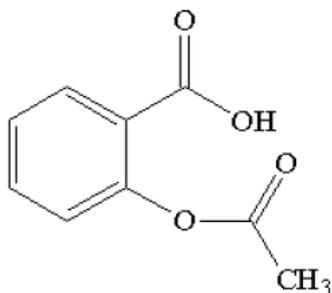
Chemical name: 2-acetoxybenzoic acid (commonly known as acetylsalicylic acid)

Molecular formula: C₉H₈O₄

CAS number: 50-78-2

Molecular weight: 180.2

Structural formula:



DESCRIPTION

Dipyridamole

Dipyridamole is an odourless, yellow crystalline powder with a bitter taste. It has a melting point in the range of 164-168°C, and is soluble in dilute acids, methanol, ethanol and chloroform.

Aspirin

Aspirin is a white crystalline powder or colourless crystals, odourless or almost odourless, slightly soluble in water, freely soluble in alcohol, soluble in chloroform and in ether. It melts at about 143°C.

The excipients in ASASANTIN SR sustained-release capsules are: tartaric acid, povidone, methacrylic acid copolymer (Eudragit S 100), talc, acacia, hypromellose, hypromellose phthalate, glycerol triacetate, dimethicone 350, stearic acid, lactose, aluminium stearate, colloidal anhydrous silica, maize starch, microcrystalline cellulose, sucrose, gelatin, titanium dioxide, iron oxide red CI77491 and iron oxide yellow CI77492.

PHARMACOLOGY

Pharmacotherapeutic group: ANTITHROMBOTIC AGENTS - Platelet aggregation inhibitors excl. heparin

ATC code: B01AC07 (dipyridamole)
B01AC06 (acetylsalicylic acid)

Dipyridamole has an antithrombotic action based on its ability to modify various aspects of platelet function. It causes inhibition of platelet adhesion and aggregation, particularly in diseased states where platelet stickiness is above normal, and lengthens abnormally shortened platelet survival time. These actions are useful in limiting the initiation of thrombus formation. The mechanism of antiplatelet action is believed to be related to inhibition of the uptake of adenosine by red blood cells and platelets; weak inhibition of cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE) which potentiates the aggregation-inhibiting effects of adenosine on platelets; and inhibition of cyclic guanosine monophosphate-PDE (cGMP-PDE) which potentiates the anti-aggregating effects of EDRF (endothelium derived relaxing factor, identified as nitric oxide (NO)). Dipyridamole is also a coronary vasodilator.

Dipyridamole has also been shown in stroke patients to reduce the density of prothrombotic surface proteins (PAR-1: Thrombin receptor) on platelets as well as to reduce levels of c-reactive protein (CRP) and von Willebrand Factor (vWF). *In-vitro* investigations have shown that dipyridamole inhibits inflammatory cytokines (MCP-1 and MMP-9) arising from platelet-monocyte interaction.

Dipyridamole increases the release of Tissue Plasminogen Activator from microvascular endothelial cells (human brain, *in vitro*, concentration-dependent) and is likely to lead to increased fibrinolytic /anti-thrombotic activity. Dipyridamole is a potent scavenger of oxy- and peroxy-radicals.

Aspirin inhibits platelet aggregation by its irreversible acetylation of cyclo-oxygenase, which effectively blocks the activity of this enzyme in platelets.

The anti-thrombotic effects of dipyridamole and aspirin are additive.

Pharmacokinetics

Absorption

Dipyridamole

Plasma concentrations of dipyridamole from the ASASANTIN SR formulation rise after a lag time of about 30 minutes. Steady state conditions are generally reached within 3 days. Peak plasma concentrations at steady state conditions are reached at about 2-3 hours, and then decline slowly. Peak concentrations of dipyridamole from the ASASANTIN SR formulation administered twice

daily are about 1.76 (1.22-2.71) µg/mL. There is no accumulation with repetitive dosing. The decline in plasma concentration after oral administration fits a two compartment model. The alpha half life (the initial decline following peak plasma concentration), which represents elimination of the majority of administered drug, has been reported to be about 30-60 minutes and the beta half life (the terminal decline in plasma concentration) is approximately 10-12 hours. Total plasma clearance has been reported to be about 12 L/hr. Dipyridamole may undergo entero-hepatic recirculation. The absolute bioavailability is limited by first pass hepatic metabolism and incomplete oral absorption and is about 70%.

Aspirin

Aspirin is absorbed rapidly from the gastrointestinal tract following oral administration. Approximately 30% of the dose of aspirin is hydrolysed presystemically to salicylate. Peak plasma concentrations at steady state conditions of aspirin are reached at 0.5 (0.5-1) hours after administration. Peak concentrations with 25 mg twice daily are about 200 (133-300) ng/mL. Peak plasma concentrations at steady state conditions of salicylic acid are reached at 1-1.5 hours after administration. Peak concentrations with 25 mg twice daily are about 1330 (990-1900) ng/mL.

Distribution

Dipyridamole

Animal studies have shown that dipyridamole is widely distributed, preferentially to the liver, lungs, kidney, spleen and heart. In man, the apparent volume of distribution is about 140 litres, and 97-99% of the drug is bound to plasma protein. Dipyridamole does not cross the blood-brain barrier. Placental transfer of dipyridamole is very low. It is known to be excreted into breast milk.

Aspirin

After absorption aspirin is rapidly converted to salicylate, but during the first 20 minutes following oral administration, aspirin is the predominant form of the drug in the plasma. Plasma aspirin concentrations decline rapidly with a half-life of approximately 15 minutes.

Salicylic acid is 80-90% bound to plasma proteins and is widely distributed. The volume of distribution of salicylates is reported to be approximately 10 L body-weight in adults. Although both aspirin and salicylate have pharmacological activity, only aspirin has an anti-platelet effect. Salicylate is extensively bound to plasma proteins and is rapidly distributed to all body tissues. Salicylate appears in breast milk and crosses the placenta.

Metabolism and excretion

Dipyridamole

Dipyridamole is metabolised in the liver predominantly to form a monoglucuronide which is excreted in the bile. In plasma about 70-80% of the total amount is present as parent compound and 20-30% as the monoglucuronide. Renal excretion is about 5%.

Aspirin

Salicylate is mainly eliminated by hepatic metabolism; the major metabolites include salicylic acid, salicyl phenolic glucuronide and salicylic acyl glucuronide, and the minor metabolites are gentisic acid and gentisuric acid. The formation of the major metabolites salicylic acid and salicyl phenolic glucuronide is easily saturated and, as a result, steady-state plasma salicylate concentrations increase disproportionately with dose; the other metabolic routes are first-order process. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH, about 30% of a dose being excreted in alkaline urine compared with 2% of a dose in acidic urine. Aspirin has an elimination half-life of 15-20 minutes in plasma; the major metabolite salicylic acid has a half-life of elimination of 2-3 hours at low doses, which may rise to 30 hours at higher doses because of nonlinearity in metabolism and plasma protein binding.

CLINICAL TRIALS

The second European Stroke Prevention Study (ESPS2) was conducted to investigate the effect of sustained-release dipyridamole 200 mg twice daily and low-dose aspirin 25 mg twice daily, alone or in combination, for the indications prevention of secondary stroke and transient ischaemic attacks (TIAs). This was a multicentre, multinational, randomised, double-blind, placebo-controlled trial in patients (n=6602) who had experienced a recent ischaemic stroke or TIA. There were 4 parallel treatment groups organised in a 2x2 factorial design with each treatment given for 2 years. Treatments were: placebo; aspirin 25 mg twice daily; PERSANTIN® SR (dipyridamole 200 mg) twice daily; and ASASANTIN SR (dipyridamole 200 mg with aspirin 25 mg) twice daily. The mean age of the patients was 66.7 years. The qualifying event was TIA in 23.7% of patients and stroke in 73.6% of patients.

The three primary endpoints were: stroke (fatal or not); death from any cause; and stroke and/or death occurring within 2 years of inclusion in the study. Secondary endpoints were myocardial infarction, ischaemic events, other vascular events, vascular deaths, vascular events and TIA. Endpoint data were analysed by calculating for each endpoint the “survival” curves of the four treatment groups. The Cox model was used to identify covariates with significant negative or positive impact upon “survival”.

In terms of stroke prevention, the results showed highly significant differences between the four survival curves ($p < 0.001$). Factorial analysis showed that both drugs were effective ($p < 0.001$), without interaction of one treatment upon the other, and that both given together were additive. Pairwise comparisons demonstrated that the combined therapy with dipyridamole and aspirin resulted in more effective stroke prevention (risk reduction = 37%, $p < 0.001$, 157/1650) than treatment with either aspirin alone (risk reduction = 18%, $p < 0.01$, 206/1649) or dipyridamole alone (risk reduction = 16%, $p < 0.01$, 211/1654), compared to placebo (250/1649). Combined therapy with dipyridamole and aspirin reduced the risk of stroke by 23.1% ($p = 0.006$) when compared to aspirin therapy alone, and reduced the risk of stroke by 24.7% ($p = 0.002$) when compared to dipyridamole alone therapy. Subgroup analysis based upon demographic criteria, the type of qualifying event or associated risk factors, corroborated the significant treatment effects observed in the total trial population. Subjects who already had a history of cerebrovascular accidents before the qualifying event, had a greater risk reduction of further stroke with combined therapy (48% [$p < 0.001$ compared to placebo]) than subjects in which the qualifying event was the first cerebrovascular accident (29% [$p < 0.01$ compared to placebo]). Subgroup analysis also showed that aspirin and/or dipyridamole were only effective in preventing non-fatal stroke, in contrast to fatal stroke which was not influenced by the treatment. Cox analysis of the “survival” data identified history of a previous cerebrovascular accident before the qualifying event as the most important risk factor predisposing to stroke recurrence, followed by daily alcohol consumption of > 5 units/day, diabetes and atrial fibrillation. The same analysis showed that receiving dipyridamole or receiving aspirin were strongly protecting against stroke.

Neither aspirin nor dipyridamole influenced mortality significantly. Effects of dipyridamole and/or aspirin on protection from endpoint stroke and/or death were similar to the effects on stroke. In addition to the prevention of stroke, dipyridamole and/or aspirin were effective in preventing subsequent TIAs, especially in the subgroup of patients in whom TIA was the qualifying event. As was observed for stroke, the efficacy of aspirin and dipyridamole when co-prescribed was additive, being double that of either drug alone. Other relevant events from which occurrence was modified by treatment included ischaemic events, vascular events, and other vascular events (mostly deep venous thrombosis or peripheral arterial occlusion).

The ESPS2 trial shows the efficacy of both sustained-release dipyridamole and low-dose aspirin in preventing stroke. Stroke prevention is even more effective when aspirin and dipyridamole are combined, the benefit being additive. The study also shows that such therapy can prevent recurrence of TIA in patients with a previous history of TIA or stroke.

The results of the ESPS2 study are supported by the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) study that studied a combination treatment of dipyridamole 200 mg twice daily (83% of patients treated with the extended release dipyridamole formulation) and aspirin 30-325 mg daily. A total of 2739 patients who had experienced ischaemic stroke of

arterial origin were enrolled in the aspirin-alone (n=1376) and combination aspirin plus dipyridamole (n=1363) arms. The primary outcome event was the composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complications, whichever occurred first. In the intention-to-treat analysis, patients in the aspirin plus dipyridamole group showed a 20% risk reduction ($p < 0.05$) for the primary composite end point compared with those in the aspirin alone group (12.7% [173/1363] versus 15.7% [216/1376]; hazard ratio [HR] 0.80, 95% CI 0.66-0.98).

The PRoFESS (PREvention Regimen For Effectively avoiding Second Strokes) study was a randomised, parallel group, international, double-blind, double-dummy, active and placebo controlled, 2x2 factorial study to compare ASASANTIN SR with clopidogrel, and telmisartan with matching placebo in the prevention of stroke in patients who had previously experienced an ischaemic stroke, mainly of non-cardioembolic origin. A total of 20332 patients were randomised to ASASANTIN SR (n=10181) or clopidogrel (n=10151), both given on a background of standard treatment. For the ASASANTIN SR versus clopidogrel comparison, the primary objective of the trial was to demonstrate non-inferiority of ASASANTIN SR compared to clopidogrel (non-inferiority margin 1.075) on the primary endpoint, which was the time to first recurrent stroke of any type. Hypothesis test was performed using hazard ratios and time-to-event analyses (Kaplan-Meier). The mean exposure to the antiplatelet medication was 2.0 years in the ASASANTIN SR group and 2.2 years in the clopidogrel group, reflecting a higher frequency of permanent premature discontinuation of ASASANTIN SR (35.1%) versus clopidogrel (28.9%). This difference was primarily due to the higher incidence of discontinuations due to adverse events in the ASASANTIN SR group (16.4%) than in the clopidogrel group (10.7%). Headache, dizziness, vomiting and nausea were the most commonly reported adverse events that contributed to the difference between the two treatment groups (see also ADVERSE EFFECTS).

The incidence of the primary endpoint was similar in both treatment groups (9.0% for ASASANTIN SR versus 8.8% for clopidogrel; HR 1.01, 95% CI 0.92-1.11). The primary objective of the trial in demonstrating the non-inferiority of ASASANTIN SR versus clopidogrel could not be established and therefore all secondary and tertiary endpoint analysis are considered to be exploratory in nature. For the pre-specified secondary composite endpoint of recurrent stroke, myocardial infarction, or death due to vascular causes, similar rates were observed between the ASASANTIN SR and clopidogrel treatment groups (13.1% in both treatment groups).

INDICATIONS

ASASANTIN SR sustained-release capsules are indicated for the prevention of recurrent ischaemic stroke and transient ischaemic attacks.

CONTRAINDICATIONS

- Hypersensitivity to any of the components of the product or salicylates
- Patients with rare hereditary problems of fructose intolerance and/or galactose intolerance (e.g. galactosaemia) should not take this medicine. Each ASASANTIN SR capsule contains 53 mg lactose and 11.3 mg sucrose resulting in 22.6 mg sucrose and 106 mg of lactose per maximum recommended daily dose.
- Concurrent use with ketorolac
- Severe renal impairment
- Patients with active gastric or duodenal ulcers or bleeding disorders
- Patients in the last trimester of pregnancy (see PRECAUTIONS: Effects on fertility, Use in pregnancy and Use in lactation)

PRECAUTIONS

Bleeding Disorders

Due to the risk of bleeding, as with other antiplatelet agents, ASASANTIN SR should be used with caution in patients at increased bleeding risk and patients should be followed carefully for any signs of bleeding, including occult bleeding (see INTERACTIONS WITH OTHER MEDICINES).

Caution should be advised in patients receiving concomitant medication which may increase the risk of bleeding, such as anticoagulants, antiplatelet agents, selective serotonin reuptake inhibitors (SSRIs), or anagrelide (see INTERACTIONS WITH OTHER MEDICINES).

Cardiovascular Disorders

Because dipyridamole is a potent vasodilator, high doses should be used with caution in patients with severe coronary artery disease (e.g. unstable angina or recently sustained myocardial infarction), subvalvular aortic stenosis, or haemodynamic instability (e.g. decompensated heart failure).

Myasthenia Gravis

In patients with myasthenia gravis, readjustment of therapy may be necessary after changes in dipyridamole dosage (see INTERACTIONS WITH OTHER MEDICINES).

Biliary Disorders

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 unconjugated dipyridamole in bile may be the mechanism responsible for the presence of dipyridamole in gallstones.

Headache or Migraine-like Headache

Headache or migraine-like headache which may occur especially at the beginning of ASASANTIN SR therapy should not be treated with analgesic doses of aspirin (see DOSAGE AND ADMINISTRATION).

Hypersensitivity

In addition, caution is advised in patients who are hypersensitive to non-steroidal anti-inflammatory drugs.

Aspirin Related Precautions

Due to the aspirin component, ASASANTIN SR should be used with caution in patients with asthma, allergic rhinitis, nasal polyps, chronic or recurring gastric or duodenal complaints, impaired renal or hepatic function (see PHARMACOLOGY: Pharmacokinetics) or glucose-6-phosphate dehydrogenase deficiency.

Aspirin has been shown to enhance the effect of anticoagulants, antiplatelet drugs, valproate and phenytoin which may result in an increased risk of side effects. The use of aspirin with selective serotonin reuptake inhibitors (SSRIs) or anagrelide may increase the risk of bleeding. Gastrointestinal side effects also increase when aspirin is administered concomitantly with NSAIDs, corticosteroids or chronic alcohol use (see INTERACTIONS WITH OTHER MEDICINES).

Effects on fertility

No studies on the effects on human fertility have been conducted. In mice, single oral doses (up to 1000 mg/kg) of a combination (1:5 ratio) of dipyridamole and aspirin did not cause impairment of male fertility.

Use in pregnancy (Category C)

Aspirin inhibits prostaglandin synthesis. When given late in pregnancy, it may cause premature closure of the fetal ductus arteriosus, delay labour and birth. Aspirin increases bleeding time both

in the newborn infant and in the mother because of its antiplatelet effects. Products containing aspirin should be avoided in the last trimester.

Reproduction studies in rats and rabbits with dipyridamole and aspirin (1:4.4) showed enhanced fetal loss at oral doses of 405.5 and 135 mg/kg/day, respectively. Maternal weight loss was also reported at these dose levels. The maximum exposure to dipyridamole in these studies was approximately equal to the human exposure to dipyridamole at the maximum recommended clinical dose, based on body surface.

Animal studies covering the peri-postnatal period have not been performed with the combination.

There are, however, no adequate and well controlled studies in pregnant women with dipyridamole and aspirin. Because animal reproduction studies are not always predictive of human response, ASASANTIN SR should only be administered during first and second trimester of pregnancy when the potential benefits for the mother outweigh the possible risks for the fetus.

ASASANTIN SR is contraindicated in the third trimester of pregnancy.

Use in lactation

Dipyridamole and salicylates are excreted in breast milk (see PHARMACOLOGY: Pharmacokinetics). Chronic high doses of aspirin can cause adverse effects in the infant.

Although the dose of aspirin in ASASANTIN SR is relatively low, caution should be used when ASASANTIN SR is administered to nursing mothers.

ASASANTIN SR should only be used in lactating women when the potential benefits for the mother outweigh the possible risks to the newborn.

Paediatric use

ASASANTIN SR is not recommended for children.

There is a possible association between aspirin and Reye's syndrome when given to children. Therefore, ASASANTIN SR should not be used in children and adolescents with feverish diseases or viral infections with or without fever, because of the risk of Reye's syndrome. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal.

Genotoxicity

Dipyridamole and aspirin (1:4) were not genotoxic in assays for gene mutations (bacteria and mammalian cells) and chromosomal aberrations.

Carcinogenicity

The carcinogenic potential was investigated in rats and mice at maximum doses of 450 mg/kg/day, divided as 75 mg/kg/day dipyridamole and 375 mg/kg/day aspirin. There was no indication of carcinogenic potential.

Stress testing with intravenous dipyridamole

Patients treated with regular oral doses of ASASANTIN SR should not receive additional intravenous dipyridamole. If pharmacological stress testing with intravenous dipyridamole is considered necessary, drugs containing oral dipyridamole (e.g. ASASANTIN SR, PERSANTIN) should be discontinued for 24 hours prior to being treated with intravenous dipyridamole. Intake of oral dipyridamole 24 hours prior to stress testing with intravenous dipyridamole may impair the sensitivity of the test.

Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. Patients should be advised that symptoms such as dizziness and confusional state have been reported in clinical trials. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience such symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

INTERACTIONS WITH OTHER MEDICINES

Drugs affecting bleeding

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.

Aspirin has been shown, when given with anticoagulants, antiplatelet drugs, selective serotonin reuptake inhibitors (SSRIs), or anagrelide to increase the risk of bleeding.

Anticoagulants

Aspirin have been shown to enhance the effect of anticoagulants which may increase the risk of bleeding.

Antiplatelet agents

The effects of ASASANTIN SR and other drugs which inhibit platelet aggregation may be additive, leading to an increased risk of bleeding.

Selective serotonin reuptake inhibitors (SSRIs)

Concurrent use of aspirin and SSRIs may increase the risk of bleeding.

Thrombolytic agents

Aspirin with PERSANTIN SR increases the risk of bleeding in patients receiving thrombolytic agents. ASASANTIN SR and thrombolytic agents should be used concurrently only with extreme caution and patients should be closely monitored for evidence of internal or external bleeding.

Diltiazem

Diltiazem enhances the inhibitory effect of aspirin on platelet aggregation and may increase the risk of bleeding.

Ethanol

Ethanol potentiates aspirin-induced prolongation of bleeding time and may increase gastrointestinal blood loss due to irritation by aspirin.

Quinidine

Quinidine may increase the inhibitory effect of aspirin on platelet aggregation and may increase the risk of bleeding.

Verapamil

Verapamil may inhibit platelet aggregation and increase the risk of bleeding if combined with ASASANTIN SR.

Drugs affecting the cardiovascular system

Antihypertensive agents

Dipyridamole may increase the hypotensive effect of blood pressure lowering drugs. Aspirin has been shown to decrease the effectiveness of angiotensin converting enzyme inhibitors by inhibiting the synthesis of prostaglandins.

Adenosine

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

Hypoglycaemic agents

Aspirin may increase the effect of insulin and oral hypoglycaemic agents. This is most likely with aspirin doses greater than 650 mg/day and may not be clinically significant in patients taking ASASANTIN SR, however caution should be exercised.

Drugs increasing gastrointestinal side effects

Gastrointestinal side effects also increase when aspirin is administered concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids or chronic alcohol use.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Aspirin may increase the risk of gastrointestinal side effects, including bleeding, when administered with NSAIDs. Aspirin displaces diclofenac from its binding sites, reducing diclofenac effectiveness.

The concomitant administration of ibuprofen with aspirin may limit the beneficial cardiovascular effects of aspirin in patients with increased cardiovascular risk.

Alendronate

The incidence of gastrointestinal side effects is increased in patients taking aspirin in combination with alendronate.

Corticosteroids

Aspirin may increase the risk of gastrointestinal side effects, including bleeding, when administered corticosteroids. Corticosteroids may increase the clearance of aspirin.

Pharmacokinetic interactions

Antacids

Antacids may increase urinary salicylate excretion, leading to decreased plasma salicylate levels. It is not known whether this would significantly reduce the effectiveness of ASASANTIN SR.

Corticotropin

Corticotropin may increase urinary salicylate excretion, leading to decreased plasma salicylate levels. It is not known whether this would significantly reduce the effectiveness of ASASANTIN SR.

Nicotinic acid

Aspirin may decrease the clearance and increase plasma levels of nicotinic acid.

Spiroinolactone

Aspirin may decrease the natriuretic effect of spiroinolactone.

Uricosuric agents (e.g. probenecid, sulphinyprazone)

High dose aspirin may inhibit the effect of uricosuric agents (e.g. probenecid, sulphinyprazone). The effect of ASASANTIN SR on the action of uricosuric agents may not be clinically significant.

Zafirlukast

Concurrent use of aspirin and zafirlukast may result in increased plasma levels of zafirlukast. The clinical significance of this interaction is unknown.

General

Anticonvulsants

Aspirin may alter the metabolism and protein binding of valproate, leading to increased levels of unbound drug which may result in an increased risk of side effects. Unbound valproate should be monitored in patients taking sodium valproate and ASASANTIN SR.

Aspirin has been shown to enhance the effect of phenytoin, which may result in an increased risk of side effects.

Methotrexate

Aspirin may increase the toxicity of methotrexate.

Cholinesterase inhibitors

Dipyridamole may counteract the anticholinesterase effect of cholinesterase inhibitors thereby potentially aggravating myasthenia gravis (see PRECAUTIONS).

Fluoxetine

Aspirin may produce an allergic reaction in patients known to be allergic to fluoxetine.

ADVERSE EFFECTS

Summary of the safety profile

Two large scale trials (ESPS-2, PRoFESS) enrolling a total of 26,934 patients (including 11,831 patients who were allocated to ASASANTIN SR) were used to define the safety profile of ASASANTIN SR. These data are supplemented with the extensive ASASANTIN SR post-marketing experience.

Adverse reactions at therapeutic doses of ASASANTIN SR are usually mild and transient and in most cases, adverse effects reduce or disappear as treatment is continued. The most frequently reported adverse reactions are headache (in some cases the headache is severe – migraine-like, especially at the beginning of treatment), dizziness and gastrointestinal events such as dyspepsia, diarrhoea, nausea and abdominal pain. The most important serious adverse reactions associated with ASASANTIN SR are bleeding events.

In the pivotal clinical trial ESPS-2 (N=6602, see CLINICAL TRIALS), discontinuations due to adverse events were 25%, 25%, 19% and 21% in patients treated with ASASANTIN SR, PERSANTIN SR, aspirin, and placebo, respectively. The adverse events that most commonly led to discontinuation of ASASANTIN SR were headache (10%), nausea (6%) and dizziness (5%). The most common adverse events reported in patients treated with ASASANTIN SR in the pivotal clinical trial (ESPS2) are presented in Table 1 below.

Table 1: Adverse events reported in EPSP-2

	Number (%) of patients				P*
	Placebo (n=1649)	Aspirin (n=1649)	PERSANTIN SR (n=1654)	ASASANTIN SR (n=1650)	
Headache	534 (32.4%)	546 (33.1%)	615 (37.2%)	630 (38.2%)	< 0.001
Dizziness	509 (30.9%)	481 (29.2%)	498 (30.1%)	486 (29.5%)	NS
Dyspepsia	266 (16.1%)	283 (17.2%)	274 (16.6%)	290 (17.6%)	NS
Vomiting	109 (6.6%)	93 (5.6%)	119 (7.2%)	133 (8.1%)	NS
Nausea	226 (13.7%)	204 (12.4%)	245 (14.8%)	254 (15.4%)	NS
Diarrhoea	154 (9.3%)	109 (6.6%)	254 (15.4%)	199 (12.1%)	< 0.01
Gastric pain	219 (13.3%)	242 (14.7%)	240 (14.5%)	274 (16.6%)	NS
Bleeding from any site ^a	74 (4.5%)	135 (8.2%)	77 (4.7%)	144 (8.7%)	< 0.01

* p-value (Chi-squared) differences for group homogeneity.

NS = no significant differences between treatment groups.

^a Bleeding episodes were more often moderate or severe/fatal in both regimens containing aspirin when compared to dipyridamole alone or placebo. Moderate or severe/fatal bleeds for the aspirin alone arm was 53/135 (39.3%) of the 8.2% bleeding reported; for the dipyridamole and aspirin combined arm was 60/144 (41.7%) of the 8.7% bleeding reported; for the dipyridamole only arm was 24/77 (31.2%) of the 4.2% bleeding reported; and for the placebo arm was 22/74 (29.7%) of the 4.5% bleeding reported.

In the PRoFESS trial (N=20332, see CLINICAL TRIALS), discontinuations due to adverse events were 16.4% for ASASANTIN SR and 10.7% for clopidogrel. The difference was mainly due to higher incidence of discontinuations due to headache [5.9% (n=593) versus 0.9% (n=87)], dizziness [1.3% (n=134) versus 0.5% (n=52)], vomiting [1.6% (n=158) versus 0.4% (n=37)] and nausea [1.5% (n=155) versus 0.6% (n=58)] in the ASASANTIN SR group compared to the clopidogrel group.

Analysis of the bleeding events in the patients treated with ASASANTIN SR in the two large scale trials (ESPS-2, PRoFESS) are presented in Table 2 below. Bleeding events are distributed over several System Organ Classes (SOC); a summary description of bleeding is given in Table 2.

Table 2: Bleeding events reported in ESPS-2 and PRoFESS (analysed from the treated set), broken down to any bleeding, major bleeding, intracranial haemorrhage and gastrointestinal haemorrhage

	ESPS-2		PRoFESS	
	ASASANTIN SR	Placebo	ASASANTIN SR	Clopidogrel
Patients treated (N (%))	1650 (100)	1649 (100)	10055 (100)	10040 (100)
Mean exposure (years)	1.4		1.9	2.1
Any bleeding (%)	8.7	4.5	5.3°	4.9°
Major bleeding (%)	1.6	0.4	3.3	3.0
Intracranial haemorrhage (%)	0.6	0.4	1.2*	0.8*
Gastrointestinal haemorrhage⁺ (%)	4.3	2.6	1.9°	1.6°

* PRoFESS:
ASASANTIN SR intracranial haemorrhage (1.0%) and intraocular haemorrhage (0.2%)
Clopidogrel intracranial haemorrhage (0.6%) and intraocular haemorrhage (0.2%)
° frequencies from randomised set (ASASANTIN SR: N= 10181; Clopidogrel: N=10151)
+ major events as adjudicated by independent expert committee

Adverse reactions of ASASANTIN[®] SR reported from clinical trials and post-marketing experience are listed below according to System Organ Classes.

Table of side effects

MedDRA System Organ Class	Dipyridamole and Acetylsalicylic acid Adverse reactions
Blood and lymphatic system disorders*	<ul style="list-style-type: none"> • Thrombocytopenia (reduction of platelet count), Anaemia, Iron deficiency anaemia (due to occult gastrointestinal bleeding) • Disseminated intravascular coagulation², Coagulopathy²
Cardiac disorders	<ul style="list-style-type: none"> • Tachycardia, Worsening of symptoms of coronary artery disease, Syncope • Arrhythmia²
Ear and labyrinth disorders	• Tinnitus ² , Deafness ²
Eye disorders	• Eye haemorrhage
Gastrointestinal disorders	<ul style="list-style-type: none"> • Vomiting, Nausea, Diarrhoea, Dyspepsia, Gastric ulcer, Duodenal ulcer, Gastritis erosive, Gastrointestinal haemorrhage, Abdominal pain • Gastric ulcer perforation², Duodenal ulcer perforation², Melaena², Haematemesis², Pancreatitis²
General disorders and administration site conditions	• Pyrexia ² , Hypothermia ²
Hepatobiliary disorders	<ul style="list-style-type: none"> • Dipyridamole has been shown to be incorporated into gallstones¹ • Hepatitis², Reye's syndrome²
Immune system disorders	<ul style="list-style-type: none"> • Hypersensitivity reactions (including rash, urticaria, severe bronchospasm and angio-oedema) • Anaphylactic reactions (especially in patients with asthma)²
Injury, poisoning and procedural complications	• Post-procedural haemorrhage, Procedural haemorrhage
Investigations	<ul style="list-style-type: none"> • Bleeding time prolonged • Liver function test abnormal², Blood uric acid increased (may lead to gout attacks)², Prothrombin time prolonged²
Metabolism and nutrition disorders	• Hypoglycaemia (children) ² , Hyperglycaemia ² ,

MedDRA System Organ Class	Dipyridamole and Acetylsalicylic acid Adverse reactions
	Hyperkalaemia ² , Thirst ² , Dehydration ² , Metabolic acidosis ² , Respiratory alkalosis ²
Musculoskeletal, connective tissue and bone disorder	<ul style="list-style-type: none"> • Myalgia • Rhabdomyolysis²
Nervous system disorders	<ul style="list-style-type: none"> • Haemorrhage intracranial, Dizziness, Headache, Migraine-like headache (especially at the beginning of treatment) • Agitation², Brain oedema², Lethargy², Convulsion²
Pregnancy, puerperium and perinatal conditions	<ul style="list-style-type: none"> • Prolonged pregnancy², Prolonged labour², Small for dates baby², Stillbirth², Haemorrhage in pregnancy², Postpartum haemorrhage²
Psychiatric disorders	<ul style="list-style-type: none"> • Confusional state²
Renal and urinary disorders	<ul style="list-style-type: none"> • Renal failure², Nephritis Interstitial², Renal papillary necrosis², Proteinuria²
Respiratory, thoracic and mediastinal disorders	<ul style="list-style-type: none"> • Epistaxis • Dyspnoea² Gingival bleeding², Laryngeal oedema², Hyperventilation², Pulmonary oedema², Tachypnoea²
Skin and subcutaneous tissue disorders	<ul style="list-style-type: none"> • Skin haemorrhages (including contusion, ecchymosis and haematoma) • Erythema exsudativum multiforme²
Vascular disorders	<ul style="list-style-type: none"> • Hypotension, Hot flush

*Aspirin may cause haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.

¹ Identified adverse reactions of dipyridamole monotherapy

² Identified adverse reactions of aspirin monotherapy

DOSAGE AND ADMINISTRATION

The recommended dose is one capsule twice daily, usually one in the morning and one in the evening, preferably with meals.

The capsules should be swallowed whole without chewing.

Alternative regimen in case of intolerable headaches

In the event of intolerable headaches during initial treatment, switch to one capsule at bedtime and low-dose aspirin (for example, 75-150 mg) in the morning. Because there are no long-term, clinical outcome data with this regimen and headaches become less of a problem as treatment continues, patients should return to the usual regimen as soon as possible, usually within one week (see PRECAUTIONS and ADVERSE EFFECTS).

Paediatric population

ASASANTIN SR is not recommended for children (see PRECAUTIONS: Paediatric use).

OVERDOSAGE

In case of overdose, advice can be obtained from the Poisons Information Centre (telephone 13 11 26).

Symptoms

Experience with dipyridamole overdose is limited. Symptoms such as feeling warm, flushes, sweating, restlessness, feeling of weakness, dizziness and anginal complaints can be expected. A drop in blood pressure and tachycardia might be observed.

The signs and symptoms of mild acute aspirin overdose are hyperventilation, tinnitus, nausea, vomiting, impairment of vision and hearing, dizziness and confusion. In severe poisoning, delirium, tremor, dyspnoea, sweating, bleeding, dehydration, disturbances of the acid-base balance and electrolyte composition of the plasma, hypothermia and coma may be seen.

Dizziness and tinnitus can, particularly in elderly patients, be symptoms of overdose.

Treatment

General supportive measures should be employed, including administration of activated charcoal.

Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Slow intravenous administration of xanthine derivatives (aminophylline 50-100 mg over 30 to 60 seconds) may reverse the haemodynamic effects of dipyridamole overdose. If 250 mg aminophylline does not relieve anginal complaints, sublingual nitroglycerin may be administered. Due to its wide distribution to tissues and its predominantly hepatic elimination, dipyridamole is not likely to be accessible to enhanced removal procedures.

Apart from general measures, treatment of aspirin overdosage consists chiefly of measures to accelerate the excretion (forced alkaline diuresis) and to restore the acid-base and electrolyte balance. Infusions of sodium bicarbonate and potassium chloride solutions may be given. In severe cases haemodialysis may be necessary.

PRESENTATION AND STORAGE CONDITIONS

Each ASASANTIN SR sustained-release capsule contains dipyridamole 200 mg in modified release form and aspirin 25 mg in standard release form. The gelatin shell of the capsule consists of a red opaque cap and an ivory opaque body.

Capsules are packed in white polypropylene bottles with child-resistant closures and contain desiccant. Packs contain 20*, 30*, 50*, 60 or 100* capsules.

*Not currently distributed in Australia.

Store below 30°C. Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

BOEHRINGER INGELHEIM PTY LIMITED
ABN 52 000 452 308
78 WATERLOO ROAD
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

3 December 1999

DATE OF MOST RECENT AMENDMENT

27 May 2016