

IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0002/078/001

Case No: 2020226

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Bristol-Myers Squibb

Swords, Co. Dublin, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Pravagettes 40 mg/81 mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **02/11/2006** until **31/05/2011**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pravagettes 40 mg/81 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg pravastatin sodium and 81 mg acetylsalicylic acid.
For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
The oblong tablet is yellow-coloured engraved "BMS" on one side and white to off-white engraved "5171" on the opposite side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Secondary prevention: reduction of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina pectoris and with either normal or increased cholesterol levels, where the combination of pravastatin and low dose acetylsalicylic acid is considered appropriate as an adjunct to correction of other risk factors (see section 5.1).

4.2 Posology and method of administration

Pravagettes is administered orally once daily preferably in the evening with or without food.

Adults

The recommended dose is one tablet per day. The maximum recommended daily dose of pravastatin is 40 mg. In all preventive morbidity and mortality trials, the only starting and maintenance dose of pravastatin was 40 mg daily. Higher doses of ASA are required for initiating antiplatelet treatment at the acute phase of myocardial infarction and unstable angina (see section 4.4).

Children:

Pravagettes should not be given to children and adolescents under 18 years of age (see section 4.4).

Elderly patients

There is no dose adjustment necessary in these patients unless there are predisposing risk factors (see section 4.4).

Renal or hepatic impairment

Pravagettes is contraindicated in patients with severe hepatic or renal insufficiency (see section 4.3). Caution should be exercised in patients with mild or moderate hepatic or renal insufficiency (see sections 4.4 and 5.2).

Concomitant therapy

The lipid lowering effects of pravastatin on total cholesterol and LDL-cholesterol are enhanced when combined with a bile acid-binding resin (e.g. colestyramine, colestipol). Pravagettes should be given either one hour before or at least four hours after the resin (see section 4.5).

For patients taking ciclosporin with or without other immunosuppressive medicinal products, treatment should begin with 20 mg of pravastatin once daily and titration to 40 mg should be performed with caution (see section 4.5).

4.3 Contraindications

Hypersensitivity to any of the excipients.

Pravastatin

Hypersensitivity to pravastatin.

Active liver disease including unexplained persistent elevations of serum transaminase elevation exceeding 3 x the upper limit of normal (ULN) (see section 4.4).

Pregnancy and lactation (see section 4.6).

ASA

Active peptic ulcer and/or gastrointestinal haemorrhages (see section 4.4).

Gastric patients, and patients who have experienced gastric pain when previously using the medicine.

A history of haemorrhagic cerebrovascular accident.

Hypersensitivity to salicylic acid compounds, such as ASA, or prostaglandin synthetase inhibitors (e.g. some asthma patients, who may suffer an asthma attack or faint).

Severe hepatic or renal insufficiency.

Haemorrhagic diathesis or coagulation disorders, such as haemophilia and hypoprothrombinaemia.

Glucose-6-phosphatedehydrogenase deficiency (G6Pd deficiency).

Methotrexate used at doses > 15 mg/week (see section 4.5).

4.4 Special warnings and precautions for use

Pravagettes alone is not for the treatment of the acute phase of myocardial infarction or unstable angina pectoris, as a higher dose of ASA may be required for initiating antiplatelet treatment.

Pravastatin

Pravastatin has not been evaluated in patients with homozygous familial hypercholesterolaemia. Therapy is not suitable when hypercholesterolaemia is due to elevated HDL-Cholesterol.

As for other HMG-CoA reductase inhibitors, combination of pravastatin with fibrates is not recommended.

Hepatic disorders

As with other lipid-lowering agents, moderate increases in liver transaminase levels have been observed. In the majority of cases, liver transaminase levels have returned to their baseline value without the need for treatment discontinuation. Special attention should be given to patients who develop increased transaminase levels and therapy should be discontinued if increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) exceed three times the upper limit of normal and persist.

Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion.

Muscle disorders

As with other HMG-CoA reductase inhibitors (statins), pravastatin has been associated with the onset of myalgia, myopathy and very rarely, rhabdomyolysis. Myopathy must be considered in any patient under statin therapy presenting with unexplained muscle symptoms such as pain or tenderness, muscle weakness, or muscle cramps. In such cases creatine kinase (CK) levels should be measured (see below). Statin therapy should be temporarily interrupted when CK levels are > 5 x ULN or when there are severe clinical symptoms.

Very rarely (in about 1 case over 100,000 patient-years), rhabdomyolysis occurs, with or without secondary renal insufficiency.

Rhabdomyolysis is an acute potentially fatal condition of skeletal muscle which may develop at any time during treatment and is characterised by massive muscle destruction associated with major increase in CK (usually > 30 or 40 x ULN) leading to myoglobinuria.

The risk of myopathy with statins appears to be exposure-dependent and therefore may vary with individual drugs (due to lipophilicity and pharmacokinetic differences), including their dosage and potential for drug interactions. Although there is no muscular contraindication to the prescription of a statin, certain predisposing factors may increase the risk of muscular toxicity and therefore justify a careful evaluation of the benefit/risk and special clinical monitoring. CK measurement is indicated before starting statin therapy in these patients (see below).

The risk and severity of muscular disorders during statin therapy is increased by the co-administration of interacting medicines. The use of fibrates alone is occasionally associated with myopathy. The combined use of a statin and fibrates should generally be avoided. The co-administration of statins and nicotinic acid should be used with caution. An increase in the incidence of myopathy has also been described in patients receiving other statins in combination with inhibitors of cytochrome P450 metabolism. This may result from pharmacokinetic interactions that have not been documented for pravastatin (see section 4.5). When associated with statin therapy, muscle symptoms usually resolve following discontinuation of statin therapy.

Creatine kinase measurement and interpretation

Routine monitoring of creatine kinase (CK) or other muscle enzyme levels is not recommended in asymptomatic patients on statin therapy. However, measurement of CK is recommended before starting statin therapy in patients with special predisposing factors, and in patients developing muscular symptoms during statin therapy, as described below. If CK levels are significantly elevated at baseline (> 5 x ULN), CK levels should be re-measured about 5 to 7 days later to confirm the results. When measured, CK levels should be interpreted in the context of other potential factors that can cause transient muscle damage, such as strenuous exercise or muscle trauma.

Before treatment initiation

Caution should be used in patients with predisposing factors such as renal impairment, hypothyroidism, previous history of muscular toxicity with a statin or fibrate, personal or familial history of hereditary muscular disorders, or alcohol abuse. In these cases, CK levels should be measured prior to initiation of therapy. CK measurement should also be considered before starting treatment in persons over 70 years of age especially in the presence of other predisposing factors in this population. If CK levels are significantly elevated (> 5 x ULN) at baseline, treatment should not be started and the results should be re-measured after 5 - 7 days. The baseline CK levels may also be useful as a reference in the event of a later increase during statin therapy.

During treatment

Patients should be advised to report promptly unexplained muscle pain, tenderness, weakness or cramps. In these cases, CK levels should be measured. If a markedly elevated (> 5 x ULN) CK level is detected, statin therapy must be interrupted. Treatment discontinuation should also be considered if the muscular symptoms are severe and cause daily discomfort, even if the CK increase remains ≤ 5 x ULN. If symptoms resolve and CK levels return to normal, then reintroduction of statin therapy may be considered at the lowest dose and with close monitoring. If a hereditary muscular disease is suspected in such patients, restarting statin therapy is not recommended.

ASA

Concomitant treatment with anticoagulants (coumarin derivatives, heparin) is not recommended and should generally be avoided. If concurrent use cannot be avoided, frequent monitoring of the International Normalisation Ratio (INR) is indicated and patients should be cautioned to watch for signs of bleeding, especially in the gastrointestinal tract.

Close medical monitoring is also necessary for patients with bronchial asthma, allergic rhinitis (ASA may cause severe urticaria, angioedema, or bronchospasm).

Patients with a history of peptic ulcer disease and/or gastrointestinal haemorrhages should avoid using ASA (which can cause gastric mucosal irritation and bleeding). If bleeding signs and symptoms continue due to the ASA component, the physician may discontinue Pravagettes and switch the patient to pravastatin or another statin alone.

Caution should be exercised in patients with hepatic insufficiency (as ASA is metabolised mainly via the liver, see section 5.2) and in patients with renal failure.

The concomitant administration of this active substance with uricosuric agents like benzbromarone, probenecid, sulphinpyrazone is not recommended (see section 4.5).

ASA must be used with care in cases of very severe menstrual bleeding.

It is preferable to stop use of ASA before a surgical procedure (including tooth extraction) because of the risk of a prolonged bleeding time or an aggravation of the bleeding. The length of the interruption of the treatment should be determined on a case-by-case basis, but will usually be one week.

There is possible association between ASA and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. Pravagettes should not be given to children and adolescents aged under 18 years (see section 4.2).

Patients with hypertension should be monitored carefully.

Lactose: this product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence of clinically significant pharmacokinetic interactions when co-administering pravastatin and ASA.

Pravastatin

Fibrates: the use of fibrates alone is occasionally associated with myopathy. An increased risk of muscle related adverse events, including rhabdomyolysis, have been reported when fibrates are co-administered with other statins. These adverse events with pravastatin cannot be excluded; therefore the combined use of pravastatin and fibrates (e.g. gemfibrozil, fenofibrate) should generally be avoided (see section 4.4). If this combination is considered necessary, careful clinical and CK monitoring of patients on such regimen is required.

Colestyramine/Colestipol: concomitant administration resulted in approximately 40 to 50% decrease in the bioavailability of pravastatin. There was no clinically significant decrease in bioavailability or therapeutic effect when pravastatin was administered one hour before or four hours after colestyramine or one hour before colestipol (see section 4.2).

Ciclosporin: concomitant administration of pravastatin and ciclosporin leads to an approximately 4-fold increase in pravastatin systemic exposure. In some patients, however, the increase in pravastatin exposure may be larger. Clinical and biochemical monitoring of patients receiving this combination is recommended (see section 4.2).

Warfarin and other oral anticoagulants: bioavailability parameters at steady state for pravastatin were not altered following administration with warfarin. Chronic dosing of the two products did not produce any changes in the anticoagulant action of warfarin.

Products metabolised by cytochrome P450: pravastatin is not metabolised to a clinically significant extent by the cytochrome P450 system. This is why products that are metabolised by, or inhibitors of, the cytochrome P450 system can be added to a stable regimen of pravastatin without causing significant changes in the plasma levels of pravastatin, as have been seen with other statins. The absence of a significant pharmacokinetic interaction with pravastatin has been specifically demonstrated for several products, particularly those that are substrates/inhibitors of CYP3A4 e.g. diltiazem, verapamil, itraconazole, ketoconazole, protease inhibitors, grapefruit juice and CYP2C9 inhibitors (e.g. fluconazole).

In one of two interaction studies with pravastatin and erythromycin a statistically significant increase in pravastatin AUC (70%) and C_{max} (121%) was observed. In a similar study with clarithromycin a statistically significant increase in AUC (110%) and C_{max} (127%) was observed. Although these changes were minor, caution should be exercised when associating pravastatin with erythromycin or clarithromycin.

Other products: in interaction studies, no statistically significant differences in bioavailability were observed when pravastatin was administered with ASA, antacids (when give one hour prior to pravastatin), nicotinic acid or probucol.

ASA

The use of several platelet aggregation inhibitors, i.e. ASA, NSAIDs, ticlopidine, clopidogrel, tirofiban, eptifibatide, increases the risk of bleeding, likewise their combination with heparin and its derivatives (hirudine, fondaparinux), oral anticoagulants and thrombolytics. Clinical and biological parameters of haemostasis should be regularly monitored.

Contraindicated combinations

Methotrexate (used at doses > 15 mg/week): the combined drugs, methotrexate and ASA, increase haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by ASA. Therefore, the concomitant use of methotrexate with Pravagettes is contraindicated (see section 4.3).

Not recommended associations

Uricosurics agents (benzbromarone, probenecid, and sulphinpyrazone): reduced effect of uric acid excretion by competition of renal tubular uric acid elimination.

Therefore, the concomitant use of Pravagettes with uricosurics agents is not recommended (see section 4.4).

Combinations requiring precautions for use

Diuretics: risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment.

Corticosteroids: the concomitant administration of steroids may enhance the risk of GI bleeding or ulceration.

Methotrexate used at doses lower than 15 mg/week: the combined drugs, methotrexate and ASA, increased haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by ASA. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring in the presence of even mildly impaired renal function, as well as in elderly.

Heparin used at curative dosage or in elderly patients: when ASA is coadministered with heparin at curative dosage or in elderly patients, there is an increased risk of bleeding. Close monitoring of the INR, aPTT and/or bleeding time should be performed in the case of concomitant administration of both drugs.

Combinations to be taken into account

Other anticoagulants (coumarin derivatives, heparin at preventive dosage), **other platelet anti-aggregants and other thrombolytics:** increased risk of bleeding.

NSAIDs: increased risk of bleeding and of damage on gastrointestinal mucosa and enhancement of prolonging bleeding time.

Antacids: antacids can increase the renal excretion of ASA by alkalinising the urine.

Alcohol: addition of their own damage on gastrointestinal mucosa and enhancement of prolonging bleeding time.

4.6 Pregnancy and lactation

Pravagettes is contraindicated during pregnancy and lactation (see section 4.3).

Pregnancy

Pravastatin: pravastatin is contraindicated during pregnancy and should be administered to women of childbearing potential only when these patients are unlikely to conceive and have been informed of the potential risk. If a patient plans to become pregnant or becomes pregnant, the doctor has to be informed immediately and pravastatin should be discontinued because of the potential risk to the foetus.

ASA:

Effects of ASA can include inhibition of labour; premature (intra-uterine) closure of ductus arteriosus; pulmonary hypertension of the neonate and insufficiency of the tricuspid valve; renal injury with possible renal insufficiency and oligohydranios; and blood clotting.

Lactation

Pravastatin and ASA are excreted in small amounts in human breast milk.

4.7 Effects on ability to drive and use machines

Pravagettes has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects**Pravagettes**

Across the five secondary prevention studies included in the meta-analysis (CARE, LIPID, REGRESS, PLAC I, PLAC II) the combined use of ASA and pravastatin (N = 5,888) was not associated with any increases in adverse reactions when compared to either pravastatin (N = 1,436) or ASA (N = 5,833) alone. There were no significant differences in adverse reactions between genders or age groups.

The frequencies of adverse events are ranked according to the following: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$).

Pravastatin

Clinical trials: pravastatin has been studied at 40 mg in seven randomised, double-blind, placebo-controlled trials involving over 21,000 patients treated with pravastatin (N = 10,764) or placebo (N = 10,719), representing over 47,000 patient years of exposure to pravastatin. Over 19,000 patients were followed for a median of 4.8 - 5.9 years.

The following adverse drug reactions were reported; none of them occurred at a rate in excess of 0.3% in the pravastatin group compared to the placebo group.

Nervous system disorders:

Uncommon: dizziness, headache, sleep disturbance, insomnia

Eye disorders:

Uncommon: vision disturbance (including blurred vision and diplopia)

Gastrointestinal disorders:

Uncommon: dyspepsia/heartburn, abdominal pain, nausea/vomiting, constipation, diarrhoea, flatulence

Skin and subcutaneous tissue disorders:

Uncommon: pruritus, rash, urticaria, scalp/hair abnormality (including alopecia)

Renal and urinary disorders:

Uncommon: abnormal urination (including dysuria, frequency, nocturia)

Reproductive system and breast disorders:

Uncommon: sexual dysfunction

General disorders:

Uncommon: fatigue

Events of special clinical interest

Skeletal muscle: effects on the skeletal muscle, e.g. musculoskeletal pain including arthralgia, muscle cramps, myalgia, muscle weakness and elevated CK levels have been reported in clinical trials. The rate of myalgia (1.4% pravastatin vs 1.4% placebo) and muscle weakness (0.1% pravastatin vs < 0.1% placebo) and the incidence of CK level > 3 x ULN and > 10 x ULN in CARE, WOSCOPS and LIPID was similar to placebo (1.6% pravastatin vs 1.6% placebo and 1.0% pravastatin vs 1.0% placebo, respectively) (see section 4.4).

Liver effects: elevations of serum transaminases have been reported. In the three long-term, placebo-controlled clinical trials CARE, WOSCOPS and LIPID, marked abnormalities of ALT and AST (> 3 x ULN) occurred at similar frequency (≤ 1.2%) in both treatment groups.

Post marketing

In addition to the above the following adverse events have been reported during post marketing experience of pravastatin:

Nervous system disorders:

Very rare: peripheral polyneuropathy, in particular if used for long period of time, paresthesia

Immune system disorders:

Very rare: hypersensitivity reactions: anaphylaxis, angioedema, lupus erythematosus-like syndrome

Gastrointestinal disorders:

Very rare: pancreatitis

Hepatobiliary disorders:

Very rare: jaundice, hepatitis, fulminant hepatic necrosis

Musculoskeletal and connective tissue disorders:

Very rare: rhabdomyolysis, which can be associated with acute renal failure secondary to myoglobinuria, myopathy (see section 4.4)

Isolated cases of tendon disorders, sometimes complicated by rupture

ASA

The undesirable effects are often dose-dependent and are due to the pharmacological effect of ASA (see section 5.1). Most undesirable effects are usually associated with the gastrointestinal tract. Patients with known allergies or asthma are at increased risk of hypersensitivity reactions. Cross-hypersensitivity to other NSAIDs may develop.

Blood and the lymphatic disorders: Common: prolongation of the bleeding time. This effect can persist for several days after stopping the treatment and can give rise to haemorrhagic risks in the event of surgery or can lead to heavier menstruation

Uncommon: intracranial bleeding, blood in urine

Rare: haemorrhagic syndrome (nosebleeds, bleeding gums, bloody vomiting and blood loss via the faeces, etc.).

Endocrine disorders:

Very rare: hypoglycemia

Metabolism and nutrition disorders:

Very rare: Low-dose ASA can reduce the excretion of uric acid (which can lead to acute gout in pre-disposed patients)

Nervous system disorders

Rare: dizziness, headache, tinnitus. These are usually the first indications of overdose (see section 4.9)

Gastrointestinal disorders:

Very common: gastric complaints such as hyperacidity and nausea

Common: vomiting, gastritis, mild to moderate blood loss in the gastrointestinal tract, diarrhoea. With long-term or repeated use this blood loss can lead to anaemia.

Uncommon: gastric bleeding, gastric ulcers

Very rare: gastrointestinal perforation

Hepato-biliary disorders:

Very rare: liver impairment

Skin and subcutaneous tissue disorders:

Very rare: severe skin reactions (e.g. erythema exsudativum multiforme)

Renal and urinary disorders:

Very rare: acute renal insufficiency, especially in patients with existing renal insufficiency, heart decompensation, nephrotic syndrome or concomitant treatment with diuretics

Hypersensitivity reactions:

Uncommon: urticaria, skin rash, angio-oedema, rhinitis, bronchial spasms

Very rare: anaphylactic shock, aggravation of the allergic symptoms of food allergy

4.9 Overdose

Pravastatin

To date there has been limited experience with overdosage of pravastatin. There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required.

ASA

Overdosage is unlikely due to the low level of ASA in Pravagettes. However intoxication (accidental overdose) in very young children or therapeutic overdose in elderly may present as follows:

The following are associated with moderate intoxication: dizziness, headache, tinnitus, confusion and gastrointestinal symptoms (nausea, vomiting and gastric pain).

With severe intoxication, serious disturbances of the acid-base equilibrium occur. Initial hyperventilation leads to respiratory alkalosis. Subsequently a respiratory acidosis occurs as a result of a suppressive effect on the respiratory centre. A metabolic acidosis also arises due to the presence of salicylate. Given that children, infants and toddlers are often only seen at a late stage of intoxication, they will usually have already reached the acidosis stage.

The following can also arise: hyperthermia and perspiration, leading to dehydration, restlessness, convulsions, hallucinations and hypoglycaemia. Depression of the nervous system can lead to coma, cardiovascular collapse and respiratory arrest. The lethal dose of ASA is 25-30 gram. Plasma salicylate concentrations above 300 mg/l (1,67 mmol/l) suggest intoxication.

If a toxic dose has been ingested then admission to hospital is necessary. With moderate intoxication an attempt can be made to induce vomiting; if this fails, gastric lavage is indicated. Activated charcoal (adsorbent) and sodium sulphate (laxative) are then administered. Alkalisating of the urine (250 mmol NaHCO₃ for 3 hours) while monitoring the urine pH is indicated. Haemodialysis is the preferred treatment for severe intoxication. Treat other signs of intoxication symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors, other combinations, ATC-Code: C10BX02

Mechanism of action:

Pravastatin

Pravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalysing the early rate-limiting step in cholesterol biosynthesis, and produces its lipid-lowering effect in two ways. Firstly, with the reversible and specific competitive inhibition of HMG-CoA reductase, it effects modest reduction in the synthesis of intracellular cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL-cholesterol.

Secondly, pravastatin inhibits LDL production by inhibiting the hepatic synthesis of VLDL- cholesterol, the LDL-cholesterol precursor.

In both healthy subjects and patients with hypercholesterolaemia, pravastatin sodium lowers the following lipid values: total cholesterol, LDL-cholesterol, apolipoprotein B, VLDL-cholesterol and triglycerides; while HDL-cholesterol and apolipoprotein A are elevated.

ASA

The antithrombotic effect is due to the irreversible acetylating of the enzyme cyclo-oxygenase in the thrombocyte, through which the formation of the prostaglandin thromboxane A2 is inhibited. Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days) and the effect is cumulative after repeated dosing.

As a result it is possible to achieve maximum thromboxane A2 inhibition after initially higher starting dose followed by lower maintenance doses to compensate for the creation of new thrombocytes.

Clinical efficacy:

Pravastatin

Both the pravastatin and ASA components of the combination have been established separately in the prevention of cardiovascular mortality and morbidity in patients with a history of coronary heart disease (MI or angina pectoris). Their concomitant use is usually recommended in this population. Additional evidence of the benefit of this combination over each of its components is supported by a retrospective meta-analysis of five secondary prevention studies.

Table 1 compares the cardiovascular events seen in patients receiving the combination of pravastatin/ASA and ASA alone, derived from the randomised cohort in five studies (LIPID, CARE, REGRESS, PLAC I, and PLAC II) including a total of 14,617 patients).

Table 1: Number of events and risk reduction of pravastatin/ASA compared to ASA alone			
Event	Pravastatin/ASA (N = 5,888)	Placebo/ASA (N = 5,833)	Risk reduction (95% CI)
Number (%) of patients			
Fatal or nonfatal MI	445 (7.6)	626 (10.7)	31% (22, 39)
CHD death or nonfatal MI	597 (10.1)	830 (14.2)	31% (23, 38)
Ischemic stroke	134 (2.3)	183 (3.1)	29% (12, 43)
CHD death, nonfatal MI or revascularisation procedures	1,218 (20.7)	1,543 (26.5)	24% (18, 30)
CHD death, nonfatal MI, revascularisation procedures or ischemic stroke	1,314 (22.3)	1,661 (28.5)	24% (19, 30)

Table 2 compares the cardiovascular events seen in patients receiving the combination of pravastatin/ASA and pravastatin alone, derived from the non-randomised cohort not receiving ASA in the five trials.

Table 2: Number of events and risk reduction of pravastatin/ASA compared to pravastatin alone			
Event	Pravastatin/ASA (N = 5,888)	Pravastatin alone (N = 1,436)	Risk reduction (95% CI)
Number (%) of patients			
Fatal or nonfatal MI	445 (7.6)	125 (8.7)	26% (10, 39)
CHD death or nonfatal MI	597 (10.1)	196 (13.7)	37% (25, 46)
Ischemic stroke	134 (2.3)	44 (3.1)	31% (3, 51)
CHD death, nonfatal MI or revascularisation procedures	1,218 (20.7)	308 (21.5)	11% (-0.6, 22)
CHD death, nonfatal MI, revascularisation procedures or ischemic stroke	1,314 (22.3)	341 (23.8)	14% (2, 23)

In a supportive analysis, the effects of pravastatin/ASA were sustained through five years of follow-up.

Elderly:

Across the five studies (CARE, LIPID, REGRESS, PLAC I, PLAC II) used for the meta-analysis (see above), 35% of patients were aged 65 and older and 0.8% were aged 75 and older. The number of patients aged 65 and older in each treatment group was: 1,982 (34%) in pravastatin/ASA, 534 (37%) in pravastatin/placebo, 2,017 (35%) in placebo/ASA, and 534 (37%) in placebo/placebo. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The PROSPER study was a multi-center, randomised, double-blind, placebo-controlled trial evaluating the efficacy of pravastatin for the prevention of vascular events in 5,804 elderly patients (over 70 years of age) in primary (at high risk for vascular disease) and secondary (with vascular disease) prevention.

The 2,804 men (48%) and 3,000 women (52%) with a mean age of 75.3 years (range: 69-83 years) were followed for an average of 3.2 years. In the 2,565 patients with vascular disease (secondary prevention), treatment with pravastatin (with or without ASA) significantly reduced the composite cardiovascular endpoint (CHD death, nonfatal MI, and fatal plus nonfatal stroke) by 22% ($p = 0.0061$) as compared with placebo (with or without ASA).

Pravastatin (with or without ASA) showed a rate of adverse events similar to placebo. However, a significant excess of cancers was observed in the pravastatin group (8.5%) compared with the placebo group (6.8%). Such an excess of cancers was not observed in other trials of pravastatin. Sixty three percent (63%) of patients received concomitant ASA in both arms and no differences were seen in the adverse event profile and rate between both groups.

5.2 Pharmacokinetic properties

Pravagettes

Co-administration of 40 mg pravastatin and 81 mg buffered ASA produces C_{max} and AUC of pravastatin and salicylic acid not significantly different from that obtained from separate administration of both drugs, indicating no pharmacokinetic interaction between pravastatin and ASA.

Pravastatin

Absorption:

Pravastatin is administered orally in the active form. It is rapidly absorbed; peak serum levels are achieved 1 to 1.5 hours after ingestion. On average, 34% of the orally administered dose is absorbed, with an absolute bioavailability of 17%.

The presence of food in the gastrointestinal tract leads to a reduction in the bioavailability, but the cholesterol-lowering effect of pravastatin is identical whether taken with or without food.

After absorption, 66% of pravastatin undergoes a first-pass extraction through the liver, which is the primary site of its action and the primary site of cholesterol synthesis and clearance of LDL-cholesterol. *In vitro* studies demonstrated that pravastatin is transported into hepatocytes and with substantially less intake in other cells.

In view of this substantial first pass through the liver, plasma concentrations of pravastatin have only a limited value in predicting the lipid-lowering effect.

The plasma concentrations are proportional to the doses administered.

Distribution:

About 50% of circulating pravastatin is bound to plasma proteins.

The volume of distribution is about 0.5 l/kg.

A small quantity of pravastatin passes into the human breast milk.

Metabolism and elimination:

Pravastatin is not significantly metabolised by cytochrome P450 nor does it appear to be a substrate or an inhibitor of P-glycoprotein but rather a substrate of other transport proteins. Following oral administration, 20% of the initial dose is eliminated in the urine and 70% in the faeces. Plasma elimination half-life of oral pravastatin is 1.5 to 2 hours.

After intravenous administration, 47% of the dose is eliminated by the renal excretion and 53% by biliary excretion and biotransformation. The major degradation product of pravastatin is the 3- α -hydroxy isomeric metabolite. This metabolite has one-tenth to one-fortieth the HMG-CoA reductase inhibitor activity of the parent compound.

The systemic clearance of pravastatin is 0.81 l/h/kg and the renal clearance is 0.38 l/h/kg indicating tubular secretion.

Populations at risk:

Hepatic failure: systemic exposure to pravastatin and metabolites in patients with alcoholic cirrhosis is enhanced by about 50% comparatively to patients with normal liver function.

Renal impairment: no significant modifications were observed in patients with mild renal impairment. However severe and moderate renal insufficiency may lead to a two-fold increase of the systemic exposure to pravastatin and metabolites.

ASA

Absorption: After oral administration, ASA is rapidly absorbed in the proximal part of the small bowel. The maximum plasma concentration is reached after 0.5-2 hours. However, a considerable part of the dose is hydrolysed in the gastric wall during absorption.

Absorption of ASA is generally rapid and complete following oral administration. Food decreases the rate, but not the extent, of absorption of acetylsalicylic acid.

Distribution: The volume of distribution of ASA is approximately 0.20 l/kg bodyweight. The first conversion product formed from ASA, anti-inflammatorily effective salicylic acid, is bound to plasma proteins, primarily albumin, to the 90% level.

Salicylic acid diffuses slowly to the synovia and the synovial fluid. It penetrates the placenta and passes over into the maternal milk.

Metabolism: ASA is primarily converted into salicylic acid by hydrolysis. The half-life of ASA is short, approx. 15-20 minutes.

Salicylic acid is then converted into glycine acid and glucuronic acid conjugates and traces of gentisinic acid. At higher therapeutic doses the conversion capacity of salicylic acid is already exceeded and the pharmacokinetics is non-linear. This leads to a prolongation of the apparent elimination half-life of salicylic acid from a few hours to approximately 24 hours.

Elimination: Excretion is primarily via the kidneys.

The tubular resorption of salicylic acid is pH-dependent. By alkalinising the urine the proportion of unchanged salicylic acid in the excretion increases from approx. 10% to approximately 80%.

5.3 Preclinical safety data

Specific preclinical safety data for the fixed combination pravastatin and ASA are not available.

Pravastatin

Based on conventional studies of safety pharmacology, repeated dose toxicity and toxicity on reproduction, there are no other risks for the patient than those expected due to the pharmacological mechanism of action.

Repeated dose studies indicate that pravastatin may induce varying degrees of hepatotoxicity and myopathy; in general, substantive effects on these tissues were only evident at doses 50 or more times the maximum human mg/kg dose.

In vitro and *in vivo* genetic toxicology studies have shown no evidence of mutagenic potential.

In mice, a 2-year carcinogenicity study with pravastatin demonstrates at doses of 250 and 500 mg/kg/day (≥ 310 times the maximum human mg/kg dose), statistically significant increases in the incidence of hepatocellular carcinomas in males and females, and lung adenomas in females only. In rats a 2-year carcinogenicity study demonstrates at a dose of 100 mg/kg/day (125 times the maximum human mg/kg/dose) a statistically significant increase in the incidence of hepatocellular carcinomas in males only.

Reproductive toxicology studies in rats and rabbits did not produce any adverse effects on fertility or show any evidence of embryo-fetal toxicity or teratogenicity.

ASA

Mutagenic and carcinogenic potential: ASA has been assessed in many *in vitro* and *in vivo* preclinical studies. Taken together the results did not suggest any mutagenic effect. There is no evidence of carcinogenic effects for ASA in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
 Microcrystalline cellulose,
 Povidone,
 Magnesium oxide (heavy),
 Croscarmellose sodium,
 Yellow iron oxide (E 172),
 Zinc stearate,
 Calcium carbonate,
 Magnesium carbonate (heavy)
 Monobasic sodium phosphate (anhydrous),
 Corn starch,
 Citric acid (anhydrous).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Blisters: 15 months.

HDPE bottles: 24 months

6.4 Special precautions for storage

Blisters: do not store above 25°C. Store in the original package.

HDPE bottles: do not store above 25°C. Keep container tightly closed.

6.5 Nature and contents of container

Aluminium/aluminium blister packs of 14, 20, 28, 30, 50, and 98 tablets.

HDPE bottles of 30 and 90 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharmaceuticals Limited

Swords,

County Dublin

8 MARKETING AUTHORISATION NUMBER

PA 2/78/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2nd June 2006

10 DATE OF REVISION OF THE TEXT

October 2006