PRODUCT MONOGRAPH

Pr pal-Pravastatin-ASA

Acetylsalicylic acid delayed-release tablets/caplets USP
81 mg,162 mg and 325 mg

and

Pravastatin sodium tablets
10 mg, 20 mg and 40 mg

Platelet Aggregation Inhibitor

and

Lipid Metabolism Regulator

Paladin Labs Inc.   Date of Revision:
6111 Royalmount Ave. Suite #102   September 19, 2012
Montreal, Quebec
H4P 2T4

Control No. 158368

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Non-medicinal Ingredients
Oral	**pal-Pravastatin** tablet 10 mg, 20 mg, 40 mg	Lactose (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**)
Oral	**pal-ASA EC** tablet 81 mg, 162 mg	Lactose (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**)
Oral	**pal-ASA EC** **caplet, 325 mg**	Corn Starch (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**)

INDICATIONS AND CLINICAL USE

Pal-Pravastatin-ASA (Acetylsalicylic acid delayed-release and Pravastatin Sodium) is indicated in patients for whom treatment with both pal-Pravastatin and pal-ASA EC is appropriate. Please refer to Pravastatin and Acetylsalicylic acid delayed-release Product Monographs for additional information concerning approved indications.

Pal-Pravastatin-ASA is not indicated for initial therapy. The dose of pravastatin should be determined by titration before the switch to pal-Pravastatin-ASA. If the fixed combination represents the dose and dosing frequency determined by this titration, the use of pal-Pravastatin-ASA may be more convenient in the management of patients.

If during maintenance therapy dose adjustment were necessary it is advisable to use the individual drugs.

Patients receiving treatment with pal-Pravastatin-ASA should also be placed on a standard cholesterol-lowering diet and should continue on this diet during treatment.

CONTRAINDICATIONS

pal-Pravastatin

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

- Active liver disease or unexplained, persistent elevations of liver function tests (see **WARNINGS AND PRECAUTIONS**, Hepatic/Biliary/Pancreatic).

- Pregnancy and lactation (see **WARNINGS AND PRECAUTIONS**, Special Populations, Use in Obstetrics and Nursing Mothers.)

  Atherosclerosis is a chronic process and discontinutation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, pravastatin is contraindicated during pregnancy.

pal-ASA EC

- Sensitivity to the ingredients; active peptic ulcer. Patients who had a bronchospastic reaction to acetylsalicylic acid or nonsteroidal anti-inflammatory drugs.

WARNINGS AND PRECAUTIONS

Clinically significant warnings and precautions for pal-Pravastatin and pal-ASA EC are listed in alphabetical order.

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pal-Pravastatin

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General

Before instituting therapy with pravastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight and obese patients, and to treat other underlying medical problems (see **INDICATIONS AND CLINICAL USE**). The patient should be advised to inform subsequent physicians of the prior use of pravastatin.

Pravastatin may elevate creatine phosphokinase and transaminase levels. This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Carcinogenesis

A 21-month oral study in mice, with doses of 10 to 100 mg/kg daily of pravastatin did not demonstrate any carcinogenic potential. In a 2-year oral study in rats, a statistically significant increase in the incidence of hepatocellular carcinoma was observed in male rats given 100 mg/kg daily (125 times the maximum human dose) of pravastatin. This change was not seen in male rats given 40 mg/kg daily (50 times the recommended human dose) or less, or in female rats at any dose level.

Endocrine and Metabolism

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such could theoretically blunt adrenal and/or gonadal steroid production.

In one long-term study investigating the endocrine function in hypercholesterolemic patients, pravastatin exhibited no effect upon basal and stimulated cortisol levels, as well as on aldosterone secretion. Although no change was reported in the testicular function, conflicting results were observed in the analysis of sperm motility after administration of pravastatin. A case of reversible impotence has been reported in a 57-year old man administered pravastatin 20 mg/day and metoprolol. A causal relationship to therapy with pravastatin has not been established. Further studies are needed to clarify the effects of HMG-CoA reductase inhibitors

on male fertility. Furthermore, the effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with pravastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone, or cimetidine) that may decrease the levels of endogenous steroid hormones.

Effect on Lipoprotein (a): In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in the Lipoprotein (a)[Lp(a)] level. Further research is ongoing to elucidate the significance of Lp(a) variations. Therefore, until further experience is obtained, where feasible, it is suggested that measurements of serum Lp(a) be followed up in patients placed on pravastatin therapy.

Effect on CoQ10 Levels (Ubiquinone): A significant short-term decrease in plasma CoQ10 levels in patients treated with pravastatin has been observed. Longer clinical trials have also shown reduced serum ubiquinone levels during treatment with pravastatin and other HMG-CoA reductase inhibitors. The clinical significance of a potential long-term statin-induced deficiency of CoQ10 has not yet been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure.

Hepatic/Biliary/Pancreatic

HMG-CoA reductase inhibitors have been associated with biochemical abnormalities of liver function. As with other lipid-lowering agents, including non-absorbable bile acid-binding resins, increases in liver enzymes to <u>less than</u> three times the upper limit of normal have occurred during therapy with pravastatin. The significance of these changes, which usually appear during the first few months of treatment initiation, is not known. In the majority of patients treated with pravastatin in clinical trials, these increased values declined to pre-treatment levels despite continuation of therapy at the same dose.

Marked persistent increases (greater than three times the upper limit of normal) in serum transaminases were seen in 6 out of 1142 (0.5%) patients treated with pravastatin in clinical trials. The increases usually appeared 3 to 12 months after the start of therapy with pravastatin. These elevations were not associated with clinical signs and symptoms of liver disease and usually declined to pretreatment levels upon discontinuation of therapy. Patients rarely had persistent marked abnormalities possibly attributable to therapy. In the largest long-term placebo-controlled trial with pravastatin (Pravastatin Primary Prevention Study/WOSCOPS), no patient with normal liver function after 12 weeks of treatment (N = 2875 pravastatin-treated patients) had subsequent ALT elevations greater than three times the upper limit of normal on two consecutive measurements. Two of these 2875 patients treated with pravastatin (0.07%) and one of 2919 placebo patients (0.03%) had elevations of AST greater

than three times the upper limit of normal on two consecutive measurements during the 4.8 years (median treatment) of the study.

<u>Liver function tests should be performed at baseline and at 12 weeks following initiation of therapy or the elevation of dose.</u> Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. **If increases in alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) equal or exceed three times the upper limit of normal and persist, therapy should be discontinued.**

Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion. Active liver disease or unexplained serum transaminase elevations are contraindications to the use of pravastatin; if such condition develops during therapy, the drug should be discontinued.

Hypersensitivity

With pravastatin an apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, thrombocytopenia, leukopenia, hemolytic anemia, positive antinuclear antibody (ANA), erythrocytes sedimentation rate (ESR) increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever and malaise.

Although, to date, hypersensitivity syndrome has not been described as such, in few instances eosinophilia and skin eruptions appear to be associated with pravastatin treatment. If hypersensitivity is suspected pravastatin should be discontinued. Patients should be advised to report promptly any signs of hypersensitivity such as angioedema, urticaria, photosensitivity, polyarthralgia, fever, malaise.

Muscular

Elevations of creatinine phosphokinase levels (CPK [MM fraction]), myalgia, myopathy and rhabdomyolysis have been reported with the use of HMG-CoA reductase inhibitors, including pravastatin.

Effects on skeletal muscle such as myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with pravastatin.

Muscle weakness and rhabdomyolysis have been reported in patients receiving other HMG-CoA reductase inhibitors concomitantly with itraconozole and cyclosporine.

The benefits and risks of using HMG-CoA reductase inhibitors concomitantly with immunosuppressive drugs, fibrates, erythromycin, systemic azole derivative antifungal agents or lipid-lowering doses of niacin should be carefully considered.

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported with pravastatin and other HMG-CoA reductase inhibitors.

Myopathy, defined as muscle pain or muscle-weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if associated with malaise or fever. Patients who develop any signs or symptom ssuggestive of myopathy should have their CPK levels measured. Pravastatin therapy should be discontinued if markedly elevated CPK levels are measured or myopathy is diagnosed or suspected.

As with other statins, the risk of myopathy including rhabdomyolysis may be substantially increased by concomitant immunosuppressive therapy including cyclosporines, and by concomitant therapy with gemfibrozil, erythromycin or niacin.

Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with immunosupressants, fibric acid derivatives or niacin (see **DETAILED PHARMACOLOGY**.)

The use of fibrates alone is occasionally associated with myopathy. In a limited size clinical trial of combined therapy with pravastatin (40 mg/day) and gemfibrozil (1200 mg/day), myopathy was not reported, although a trend towards CPK elevations and musculoskeletal symptoms was seen. <u>The combined use of pravastatin and fibrates should generally be avoided.</u>

No information is available on the combined therapy of pravastatin with erythromycin.

Pre-disposing Factors for Myopathy/Rhabdomyolysis: pal-Pravastatin, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- Personal or family history of hereditary muscular disorders
- Previous history of muscle toxicity with another HMG-CoA reductase inhibitor
- Concomitant use of a fibrate or niacin
- Hypothyroidism
- Alcohol abuse
- Excessive physical exercise
- Age >70 years
- Renal impairment
- Hepatic impairment
- Diabetes with hepatic fatty change
- Surgery and trauma
- Frailty
- Situation where an increase in plasma levels of active ingredient may occur.

pal-Pravastatin therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of myopathy or predisposing to the development of rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic endocrine and electrolyte disorders, or uncontrolled seizures).

Ophthalmologic

Current data from clinical trials do not indicate an adverse effect of pravastatin on the human lens.

Special Populations

Use in the Elderly: Pharmacokinetic evaluation of pravastatin in patients over the age of 65 years indicates an increased AUC. There were no reported increases in the incidence of adverse effects in these or other studies involving patients in that age group. As a precautionary measure, the lowest dose should be administered.

Use in Children: Only limited experience with the use of statins in children is available. There is no experience to date with the use of pravastatin in such patients. Treatment in these patients is not recommended at this time.

Use in Obstetrics: **Pravastatin is contraindicated during pregnancy** (see **CONTRAINDICATIONS)**. Safety in pregnant women has not been established. Although pravastatin was not teratogenic in rats at doses as high as 1000 mg/kg daily nor in rabbits at doses of up to 50 mg/kg daily, pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of potential hazards. If a woman becomes pregnant while taking pravastatin, pravastatin should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A negligible amount of pravastatin is excreted in human breast milk. Because of the potential for adverse reactions in nursing infants, if the mother is being treated with pravastatin, nursing should be discontinued or treatment with pravastatin stopped.

Use in Patients with Impaired Renal Function: There have been no studies on the use of pravastatin in patients with renal failure. As a precautionary measure, the lowest dose should be used in these patients (see **WARNINGS AND PRECAUTIONS**, Muscular)

Patients with Severe Hypercholesterolemia: Higher doses (40 mg/day) required for some patients with severe hypercholesterolemia are associated with increased plasma levels of pravastatin. **Caution should be exercised in such patients who are also significantly renally impaired or elderly.** (see **WARNINGS AND PRECAUTIONS**, Muscular)

Homozygous Familial Hypercholesterolemia: Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. Most HMG-CoA reductase inhibitors are less or not effective in this subgroup of hypercholesterolemic patients.

pal-ASA EC

General

ASA should be used with extreme caution in patients with decreased renal function, bleeding tendencies, significant anemia, hypoprothrombinemia, thrombocytopenia, vitamin K deficiency or severe hepatic disease.

ASA is one of the most frequent causes of accidental poisonings in toddlers and infants. Tablets and caplets should be kept well out of the reach of children.

Use in Children: A possible association between Reye's syndrome and the use of salicylates has been suggested but not established. Reye's syndrome has also occurred in many patients not exposed to salicylates. However, caution is advised when prescribing salicylate-containing medications for children and teenagers with influenza and chickenpox.

Gastrointestinal

Gastrointestinal toxicity may occur with the use of ASA. No studies, to date, identified any group of patients not at risk of ulceration and bleeding. A history of serious gastrointestinal events and other factors such as ASA dosage, excessive alcohol intake, smoking, advanced age, female gender and concomitant corticosteroid or anticoagulant use have been associated with increased risk. Patients should be informed about the signs and symptoms of serious gastrointestinal toxicity and advised to contact their physician immediately if they occur. Because serious events can occur without warning symptoms, patients on long-term therapy should have periodic hemoglobin determinations in conjunction with vigilant follow up.

Hypersensitivity

ASA sensitivity is rare, occurring in less than 1% of the general population. It usually involves bronchospasm, urticaria, angioedema and rarely, shock and death. ASA sensitivity occurs in a higher percentage (approximately 10%) of adults with asthma, more often in women than men, and rarely in children. The syndrome of ASA-induced asthma usually begins as chronic nasal congestion with subsequent development of nasal polyps. Asthma and ASA sensitivity follow, with disease progression despite avoidance of ASA and cross-reacting drugs. The mechanism is thought to involve inhibition of intracellular cyclooxygenase (COX) in respiratory cells. Patients with ASA-induced asthma should avoid other drugs that inhibit COX, such as NSAIDs, but the majority can safely take other salicylates that do not inhibit COX enzyme (e.g., bismuth subsalicylate). Dose-dependent cross-sensitivity with acetaminophen has been reported with frequencies of up to 34%. It is recommended that patients with ASA-induced asthma use low initial doses of acetaminophen (less than 1000 mg) with monitoring for 3 hours after initial doses.

Some patients with ASA-induced asthma have been desensitized with small incremental oral doses of ASA over the course of 2 to 3 days until 400 to 650 mg is tolerated, followed by maintenance doses of 80 to 325 mg daily. Cross-desensitization to other reacting drugs also occurs when patients are desensitized to ASA.

Monitoring and Laboratory Tests

Bleeding time: ASA may prolong bleeding time for 4 to 7 days due to its effects on platelet aggregation.

Thyroid function tests: Large doses of salicylates may increase T_3 resin uptake and decrease serum concentrations of T_3 and T_4 when determined by radioimmunoassay. Salicylates may also affect TRH-induced TSH release determinations.

Salicylism

Chronic salicylate intoxication (also known as salicylism) can occur when repeated large doses (>100 mg/kg/day) are used for 2 or more days.

Special Populations

Use in Obstetrics: High doses (3 g daily) of ASA during pregnancy may lengthen the gestation and parturition time.

> **Pregnancy:** The use of full-dose ASA during pregnancy should generally be avoided, particularly in the 3rd trimester. ASA can affect hemostasis in both the mother and fetus, leading to higher risk of hemorrhage. Other possible effects include anemia and prolonged gestation and labor in the mother, and intrauterine growth retardation or premature closure of the ductus arteriosus in the fetus.

> **Lactation:** ASA is excreted in breast milk in low concentrations. Because of the potential effects of ASA on nursing infants, caution is advised if ASA is used during lactation, particularly chronic high-dose therapy.

Use in Diabetics: Diabetics receiving concurrent salicylate and hypoglycemic therapy should be monitored closely; reduction of the sulfonylurea hypoglycemic drug dosage may be necessary; insulin requirements may change.

Use in Geriatrics: Patients over 65 years of age and frail or debilitated patients are more susceptible to many adverse effects of ASA, including gastrointestinal toxicity. Consideration should be given to using lower initial doses in this patient group.

Surgery

ASA should be discontinued at least one week prior to elective surgery because of increased risk of bleeding.

ADVERSE REACTIONS

pal-Pravastatin

In seven randomized double blind placebo-controlled trials involving over 21,500 patients treated with pravastatin (N= 10,784) or placebo (N= 10,719), the safety and tolerability in the pravastatin group was comparable to that of the placebo group. Over 19,000 patients were followed for a median of 4.8 to 5.9 years, while the remaining patients were followed for two years or more.

Clinical adverse events probably or possibly related, or of uncertain relationship to therapy, occurring in at least 0.5% of patients treated with pravastatin or placebo in these long-term morbidity/mortality trials are shown in the table below:

TABLE 1

	PRAVASTATIN (N = 10,784) %	PLACEBO (N = 10,719) %
Cardiovascular		
Angina pectoris	3.1	3.4
Disturbance rhythm subjective	0.8	0.7
Hypertension	0.7	0.9
Edema	0.6	0.6
Myocardial infarction	0.5	0.7
Gastrointestinal		
Dyspepsia / heartburn	3.5	3.7
Nausea/ vomiting	1.4	1.6
Flatulence	1.2	1.1
Constipation	1.2	1.3
Diarrhea	0.9	1.1
Abdominal pain	0.9	1.0
Distention abdomen	0.5	0.5
Musculoskeletal		
Musculoskeletal Pain (includes arthralgia)	5.9	5.7
Muscle cramp	2.0	1.8
Myalgia	1.4	1.4
Musculoskeletal trauma	0.5	0.3
Nervous System		
Dizziness	2.2	2.1
Headache	1.9	1.8
Sleep disturbance	1.0	0.9
Depression	1.0	1.0
Anxiety / nervousness	1.0	1.2
Paresthesia	0.9	0.9
Numbness	0.5	0.4

	PRAVASTATIN (N = 10,784) %	PLACEBO (N = 10,719) %
General		
Fatigue	3.4	3.3
Chest pain	2.6	2.6
Weight gain	0.6	0.7
Influenza	0.6	0.5
Special senses		
Vision disturbance (includes blurred vision)	1.5	1.3
Disturbance eye (includes eye inflammation)	0.8	0.9
Hearing abnormality (includes tinnitus and hearing loss)	0.6	0.5
Lens opacity	0.5	0.4
Dermatologic		
Rash	2.1	2.2
Pruritis	0.9	1.0
Renal / Genitourinary		
Urinary abnormality (includes dysuria and nocturia)	1	0.8
Respiratory		
Dyspnea	1.6	1.6
Upper respiratory infection	1.3	1.3
cough	1.0	1.0
Sinus abnormality (includes sinusitis)	0.8	0.8
Pharyngitis	0.5	0.6

Short-term Controlled Trials

All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in placebo-controlled trials of up to four months duration are identified in the following table; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

TABLE 2

Adverse Events in > 2 Percent of Patients Treated with Pravastatin 10-40 mg in Short-Term Placebo-Controlled Trials

Body System/ Event	All Events		Events Attributed to Study Drug	
	Pravastatin (N = 900) % of patients	Placebo (N = 411) % of patients	Pravastatin (N = 900) % of patients	Placebo (N = 411) % of patients
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

* Statistically significantly different from placebo

The safety and tolerability of pravastatin at a dose of 80 mg in two controlled trials with a mean exposure of 8.6 months was similar to that of pravastatin at lower doses except that 4 out of 464

patients taking 80 mg of pravastatin had a single elevation of CK > 10X ULN compared to 0 out of 115 patients taking 40 mg of pravastatin.

Post-Market Adverse Drug Reactions

During post-marketing, the following adverse events have been reported rarely, regardless of assessment of causality for pravastatin:

Cardiovascular:
> Angiodema

Gastrointestinal:
> Abnormal stool, appetite change, cirrhosis, fatty changes in liver, hepatitis and fulminant hepatic necrosis, hepatoma, jaundice (including cholestatic), pancreatitis

General:
> Chest pain (non-cardiovascular), excess fever, hot flashes, sweating, weakness

Hypersensitivity:
> Anaphylaxis, arthralgia, arthritis, asthenia, chills, dermatomyositis, erythema multiforme, ESR increase, hemolytic anemia, malaise, positive ANA, photosensitivity, polymyalgia, purpura rheumatica, Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis

Immunologic:
> Allergy

Laboratory Tests:
> Elevated CPK have been reported.

Muscular:
> Myopathy, rhabdomyolosis

Neurologic:
> Dysfunction of particular cranial nerves (alteration of taste, facial paresis, impairment of extra-ocular movement), memory impairment, mood change including depression, paresthesia equilibrium disturbance, peripheral nerve palsy, tremor, vertigo, and sleep disturbances including insomnia and nightmares.

Pulmonary:
>   Interstitial lung disease: very rare cases of interstitial lung disease, especially with long term therapy. If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Reproductive:
>   Gynecomastia, impotence, libido change, urticaria. Cases of erectile dysfunction have been reported in association with the use of statins.

Skin:
>   Skin changes (dryness, dermatitis, pruritis, scalp/hair abnormalities)

Special Senses:
>   Eye symptoms (including dryness, itching, soreness)

Others:
The following have also been reported with other statins: hepatitis, cholestatic jaundice, anorexia, psychic disturbances including anxiety, hypospermia and hypersensitivity (**See WARNINGS AND PRECAUTIONS**).

pal-ASA EC

Gastrointestinal: (the frequency and severity of these adverse effects are dose-related): nausea, vomiting, diarrhea, gastrointestinal bleeding and/or ulceration, dyspepsia, heartburn.

Ear: tinnitus, vertigo, hearing loss.

Hematologic: leukopenia, thrombocytopenia, purpura, anemia.

Dermatologic and hypersensitivity: urticaria, angioedema, pruritus, skin eruptions, asthma, anaphylaxis.

Miscellaneous: mental confusion, drowsiness, sweating, thirst.

DRUG INTERACTIONS

pal-Pravastatin

Drug-Drug Interactions

Bile Acid Sequestrants: Preliminary evidence suggests that the cholesterol-lowering effects of pravastatin and the bile acid sequestrants, cholestyramine/colestipol are additive.

When pravastatin was administered one hour before or four hours after cholestyramine or one hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin.

Other Lipid Metabolism Regulators: Gemfibrozil, nicotinic acid and probucol do not statistically significantly affect the bioavailability of pravastatin. However, in a limited size clinical trial, a trend toward CPK elevations and musculoskeletal symptoms was seen in patients treated concurrently with pravastatin and gemfibrozil. No results are available from clinical studies involving combination of pravastatin with probucol.

Myopathy, including rhabdomyolysis, has occurred in patients who were receiving co-administration of HMG-CoA reductase inhibitors with fibric acid derivatives and niacin, particularly in subjects with pre-existing renal insufficiency (see **WARNINGS AND PRECAUTIONS**, Muscular).

Based on post-marketing surveillance, gemfibrozil, fenofibrate, other fibrates and lipid lowering doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone (see **WARNINGS AND PRECAUTIONS** - Muscular). Therefore, combined drug therapy should be approached with caution.

Other Concomitant Therapy: The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are administered with drugs that inhibit the cytochrome P-450 enzyme system. *In vitro* and *in vivo* data indicate that pravastatin is not metabolized by cytochrome P450 3A4 to a clinically significant extent. This has been shown in studies with known cytochrome P450 3A4 inhibitors.

Digoxin: Coadministration of digoxin and other HMG-CoA reductase inhibitors has been shown to increase the steady state digoxin concentrations. The potential effects of coadministration of digoxin and pravastatin are not known. As a precautionary measure, patients taking digoxin should be closely monitored.

Antipyrine: Antipyrine was used as a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Pravastatin had no effect on the pharmacokinetics of antipyrine.

Coumarin Anticoagulants: Pravastatin had no clinically significant effect on prothrombin time when administered in a study to normal elderly subjects who were stabilized on warfarin.

Antacids and Cimetidine: On the average, antacids (one hour prior to pravastatin) reduce and cimetidine increases the bioavailability of pravastatin. These changes were not statistically significant. The clinical significance of these interactions is not known but is probably minimal as judged from the interaction with food (see **DETAILED PHARMACOLOGY**).

No information is available regarding interactions with erythromycin (see **WARNINGS AND PRECAUTIONS**, Muscular).

Although specific interaction studies were not performed during clinical trials, no noticeable drug interactions were reported when pravastatin was added to diuretics, antihypertensives, angiotensin converting-enzyme (ACE) inhibitors, calcium channel blockers, or nitroglycerin.

Propranolol: Coadministration of propranolol and pravastatin reduced the AUC values by 23% and 16% respectively.

Cyclosporine: In a multicentre study, the AUC values of pravastatin were shown to be five-fold higher in the presence of cyclosporine. There was no accumulation of pravastatin after multiple doses.

<u>**pal-ASA EC**</u>

Analgesics: Concurrent long-term use of ASA and other analgesic-antipyretic agents such as acetaminophen may be associated with analgesic nephropathy (papillary necrosis and tubulointerstitial inflammation).

Antacids: Chronic high-dose use of antacids may increase renal elimination of salicylates through alkalinization of the urine.

Anticoagulants: Concomitant use of ASA and anticoagulants increases the risk of bleeding. Large doses of ASA may enhance the hypoprothrombinemic response to warfarin; however, ASA is used in selected patients with prosthetic heart valves or coronary artery disease in conjunction with warfarin, with appropriate monitoring.

Anticonvulsants: Large doses of ASA may increase phenytoin serum levels by inhibition of phenytoin metabolism. Valproic acid (VPA) may cause hypoprothrombinemia and inhibit platelet aggregation. Concomitant use of ASA and VPA may cause increased valproic acid levels and may lead to an increased risk of bleeding.

Antihyperglycemic Agents: ASA increases the antiphyperglycemic response to sulfonylureas, especially chlorpropamide. Large doses of ASA may cause a decrease in blood glucose, which may alter the insulin requirements of diabetic patients.

Corticosteroids: Corticosteroids may decrease the serum salicylate concentrations through increased excretion. Concomitant use may also increase the risk of gastrointestinal side effects.

Methotrexate: Concurrent use of ASA and methotrexate may lead to higher methotrexate serum levels, mainly through competition for renal excretion.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Concomitant use of ASA and NSAIDs increase the risk of gastrointestinal side effects while providing no additional therapeutic benefit. It has also been suggested that ibuprofen and possibly other NSAIDs antagonize the anti-platelet effects of low-dose preventive ASA therapy, and that taking the daily ASA dose 2 hours before the other NSAID may help prevent this interaction.

Uricosuric agents: ASA may decrease the urocosuric effects of sulfinpyrazone and probenecid.

Drug/Lab Test Interactions: Bleeding time: ASA may prolong bleeding time for 4 to 7 days due to its effects on platelet aggregation.

Thyroid function tests: Large doses of salicylates may increase T_3 resin uptake and decrease serum concentrations of T_3 and T_4 when determined by radioimmunoassay. Salicylates may also affect TRH-induced TSH release determinations.

DOSAGE AND ADMINISTRATION

Pal-Pravastatin-ASA

Prior to initiating pravastatin sodium, the patient should be placed on at least an equivalent of the American Heart Association (AHA) Step 1 diet, which should be continued during treatment. If appropriate, a program of weight control and physical exercise should be implemented.

Dosage must be individualized. Pal-Pravastatin-ASA is not indicated for initial therapy. The dose of pravastatin should be determined by titration before the switch to pal-Pravastatin-ASA.

The recommended starting dose of pal-Pravastatin is 10 to 20 mg once daily. If serum cholesterol is markedly elevated (i.e., severe hypercholesterolemia) (e.g., Total Cholesterol greater than 7.75 mmol/L [300 mg/dL]) dosage may be initiated at 40 mg/day.

The daily dose of pal-ASA EC is one tablet of 81mg, 162 mg or one caplet of 325 mg, taken at bedtime, with or without food. Because of the acetylsalicylic acid component, the dose should be taken with a full glass of water, unless the patient is fluid restricted.

Periodic lipid determinations should be performed and dosage adjusted according to the patient's response to therapy.

Pal-Pravastatin-ASA should be avoided in patients with severe hepatic or renal insufficiency.

OVERDOSAGE

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

pal-Pravastatin

There have been two reports of overdosage with pravastatin, both of which were asymptomatic and not associated with clinical laboratory abnormalities.

In the event of overdosage, treatment should be symptomatic and supportive, and appropriate therapy instituted. Until further experience is obtained, no specific therapy of overdosage can be recommended. The dialyzability of pravastatin and its metabolites is not known.

pal-ASA EC

Symptoms:
In mild overdosage, these may include rapid and deep breathing, nausea, vomiting, vertigo, tinnitus, flushing, sweating, thirst, arid tachycardia. In more severe cases, acid-base disturbances including respiratory alkalosis and metabolic acidosis can occur. Severe cases may show fever, hemorrhage, excitement, confusion, convulsions or coma and respiratory failure.

Treatment
Treatment consists of prevention and management of acid-base and fluid and electrolyte disturbances. Renal clearance is increased by increasing urine flow and by alkaline diuresis, but care must be taken in this approach not to aggravate further the metabolic acidosis that develops and the hypokalemia. Acidemia should be prevented by administration of adequate sodium containing fluids and sodium bicarbonate. Hypoglycemia is an occasional accompaniment of salicylate overdosage and can be managed by glucose solutions. If a hemorrhagic diathesis is evident, give vitamin K. Hemodialysis may be useful in complex acid base disturbances particularly in the presence of abnormal renal function.

ACTION AND CLINICAL PHARMACOLOGY

Pal-Pravastatin-ASA (Acetylsalicylic acid delayed-release and Pravastatin Sodium) is intended to facilitate the daily administration of its individual components, pal-ASA EC and pal-Pravastatin, when used together for the intended patient population (see **INDICATIONS AND CLINICAL USE** and **DOSAGE FORMS, COMPOSITION AND PACKAGING**). Pal-Pravastatin-ASA contains individual daily doses of pal-ASA EC 81 mg, 162 mg tablets or 325 mg caplets packed with either pal-Pravastatin 10 mg, 20 mg, or 40 mg for oral administration.

pal-ASA EC (81 and 162 mg tablets): The inhibition of platelet aggregation by ASA is due to its ability to interfere with the production of thromboxane A_2 within the platelet. Thromboxane A_2 is largely responsible for the aggregating properties of platelets.

pal-ASA EC (325 mg caplets): Acetylsalicylic acid has analgesic, antipyretic and anti-inflammatory properties.

In rheumatic diseases, although the analgesic and antipyretic effects are useful, the major purpose for which Acetylsalicylic acid is used is to reduce the intensity of the inflammatory process. Inhibition of prostaglandin synthesis may be involved in the anti-inflammatory action of Acetylsalicylic acid.

Acetylsalicylic acid also alters platelet aggregation and release reaction by inhibiting prostagiandin synthesis. Thromboxane A2 is an essential step in platelet aggregation. Acetylsalicylic acid prevents Thromboxane A2 formation by acetylation of platelet cyclooxygenase. This inhibition of prostaglandin synthesis is irreversible and affects platelet function for the life of the platelet.

The enteric coating substantially resists disintegration in aqueous fluids having a pH lower than 3.5 for a period of at least 2 hours and is capable of disintegrating in aqueous fluids having a pH of at least 5.5 in from 10 to 30 minutes. Thus, enteric coating effectively inhibits the release of Acetylsalicylic acid in the stomach, while allowing the tablet to dissolve in the upper portion of the small intestine for absorption from the duodenal area.

Clinical experience has shown that enteric-coated acetylsalicylic acid diminishes or eliminates gastric distress during long-term treatment with high doses of Acetylsalicylic acid.

Pharmacokinetic Information

Since the Acetylsalicylic acid 325 mg caplets are enteric-coated, the pharmacological effects are not immediate. Peak serum salicylate concentrations are reached 6 to 8 hours after single oral administration. This means that the Acetylsalicylic acid 325 mg caplets are more useful for chronic administration as in arthritis, than for providing prompt relief of pain and fever.

The plasma half-life of salicylate concentrations is dose-dependent being 3 to 6 hours at low doses (325 mg to 1.3 g) and 15 to 30 hours at high doses.

Pravastatin Sodium: Pravastatin sodium is one of a class of lipid-lowering compounds known as HMG-CoA reductase inhibitors (statins) that reduce cholesterol biosynthesis. These agents are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalysing the early rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate. Pravastatin is isolated from a strain of *Penicillium citrinum*. The active drug substance is the hydroxyacid form.

Pravastatin produces its lipid-lowering effect in two ways. First, as a consequence of its reversible inhibition of HMG-CoA reductase activity, it effects modest reductions in intracellular pools of cholesterol. This results in an increase in the number of Low Density Lipoproteins (LDL) - receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL. Second, pravastatin inhibits LDL production by inhibiting hepatic synthesis of Very Low Density Lipoproteins (VLDL), the LDL precursor.
Epidemiologic and clinical investigations have associated the risk of coronary artery disease (CAD) with elevated levels of Total-C, LDL-C and decreased levels of HDL-C. These abnormalities of lipoprotein metabolism are considered as major contributors to the development of the disease. Other factors, e.g. interactions between lipids/lipoproteins and endothelium, platelets and macrophages, have also been incriminated in the development of human atherosclerosis and of its complications.

In long-term, prospective clinical trials effective treatment of hypercholesterolemia/dyslipidemia has consistently been associated with a reduction in the risk of CAD.

Treatment with pravastatin has been shown to reduce circulating Total-C, LDL-C, and apolipoprotein B, modestly reduce VLDL-C and triglycerides (TG) while producing increases of

variable magnitude in HDL-C and apolipoprotein A. Clinical trials suggest that pravastatin's effect on reducing clinical events appears to incorporate both cholesterol modification and some ancillary mechanism.

Pravastatin has complex pharmacokinetic characteristics (see under **DETAILED PHARMACOLOGY**).

A comparative bioavailability study to evaluate the pharmacokinetic profile and estimate the bioequivalence of 40 mg tablets of pal-Pravastatin compared to the Reference formulation, i.e. Pravachol™ 40 mg tablets (Squibb Canada Division of Bristol-Myers Squibb Canada Inc.) was performed in 18 volunteers under *fasting* conditions. The results are summarized below.

TABLE 3: SUMMARY OF THE COMPARATIVE BIOAVAILABILITY DATA
pal-Pravastatin 40 mg tablets versus Pravachol ®) (Squibb Canada Inc.) 40 mg tablets (A single 40 mg dose - 1 x 40 mg) From measured data uncorrected for potency Geometric Mean Arithmetic Mean (CV %)

PARAMETER	TEST	REFERENCE	% RATIO OF GEOMETRIC MEANS
AUC_T (ng.h/mL)	174.454 188.395 (42.6)	169.723 187.090 (46.4)	102.79
AUC_I (ng.h/mL)	176.282 189.998 (42.1)	171.621 188.883 (46.0)	102.72
C_{max} (ng/mL)	76.994 85.435 (44.6)	75.308 90.119 (60.9)	102.24
T_{max}* (h)	1.08 (33.6)	1.07 (48.0)	---
$T_{1/2}$* (h)	2.46 (29.9)	2.61 (33.7)	---

*the T_{max} and the $T_{1/2}$ parameter are expressed as the arithmetic mean (CV%)

STORAGE AND STABILITY

Pal-Pravastatin-ASA should be stored at room temperature between 15 – 30 ºC. Protect from moisture and light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Pal-Pravastatin-ASA

Pal-Pravastatin-ASA is available in cartons containing either 30 pal-ASA EC 81 mg, 162 mg tablets or 325 mg caplets, packed with either 30 pal-Pravastatin 10 mg, 20 mg, or 40 mg tablets. Since pal-Pravastatin tablets are packaged in cold-form aluminum blisters and pal-ASA EC tablets/caplets are packaged in PVC/aluminum blisters, the two products will be presented in two separate colour-coded panels, next to one another.   Each pal-Pravastatin-ASA convenience pack contains 3 separate sleeves, each containing: 10 pal-Pravastatin tablets, each in cold-form aluminum blisters, on the blue, left panel and 10 pal-ASA EC tablets, each in PVC/aluminum blisters, on the red, right panel.

pal-Pravastatin

pal-Pravastatin (pravastatin) 10 mg : Each pink to peach rounded, rectangular-shaped, biconvex tablet debossed with a "Paladin" shield on one side and "P 10" on the other side for oral administration contains 10 mg of the medicinal ingredient pravastatin sodium and the following non-medicinal ingredients: colloidal Silicon Dioxide, Croscarmellose Sodium, Dibasic Calcium Phosphate, Iron Oxide IC07470 Red #30, Lactose Monohydrate Spray Dried, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol and Pyrrolidone/Vinyl Acetate Copolymer. Available in blister packs of 10 tablets.

pal-Pravastatin (pravastatin) 20 mg : Each yellow, rounded, rectangular-shaped, biconvex tablet debossed with a "Paladin" shield on one side and "P 20" on the other side for oral administration contains 20 mg of the medicinal ingredient pravastatin sodium and the following non-medicinal ingredients: colloidal Silicon Dioxide, Croscarmellose Sodium, Dibasic Calcium Phosphate, Iron Oxide IC07434 Yellow #10, Lactose Monohydrate Spray Dried, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol and Pyrrolidone/Vinyl Acetate Copolymer. Available in blister packs of 10 tablets.

pal-Pravastatin (pravastatin) 40 mg : Each green, rounded, rectangular-shaped, biconvex tablet debossed with a "Paladin" shield on one side and "P 40" on the other side for oral administration contains 40 mg of the medicinal ingredient pravastatin sodium and the following non-medicinal ingredients: colloidal Silicon Dioxide, Croscarmellose Sodium, Dibasic Calcium Phosphate, Lake Blend Green LB-451, Lactose Monohydrate Spray Dried, Magnesium Stearate,

Microcrystalline Cellulose, Polyethylene Glycol and Pyrrolidone/Vinyl Acetate Copolymer. Available in blister packs of 10 tablets.

pal-ASA EC

81 mg   Each white to off-white, round enteric-coated tablet contains 81 mg acetylsalicylic acid as active ingredient.
Non-medicinal ingredients *(alphabetically)*: Colloidal anhydrous silica, lactose anhydrous, methacrylic acid copolymer type C, methylated silica, methylcellulose, polyethylene glycol sorbitan tristearate, polydimethylsiloxane, pregelatinized starch, purified water, sodium bicarbonate, sodium lauryl sulphate, stearic acid, talc, titanium dioxide, triethyl citrate.

162 mg   Each white, caplet-shaped, enteric-coated tablet contains 162 mg acetylsalicylic acid as active ingredient.
Non-medicinal ingredients (*alphabetically*): Carnauba wax, colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose anhydrous, methylated silica, methylcellulose, polydextrose, polydimethylsiloxane, polyethylene glycol, plyvinyl aetate phthalate, pregelatinized starch , purified water, sodium alginate sodium bicarbonate, stearic acid triple presse powder, sureteric white, talc, titanium dioxide, triethyl citrate .

325 mg   Each capsule-shaped, yellow, film-coated enteric-coated caplets contains 325 mg acetylsalicylic acid as active ingredient.
Non-medicinal ingredients (*alphabetically*): Colloidal anhydrous silica, corn starch, guar gum, hydrogenated vegetable oil type I, iron oxide yellow, lecithin, methacrylic acid copolymer type C, methylated silica, methylcellulose, microcrystalline cellulose, polyethylene glycol sorbitan tristearate, polydimethylsiloxane, polyvinyl alcohol, sodium bicarbonate, sodium lauryl sulphate, talc, titanium dioxide, triethyl citrate, water.

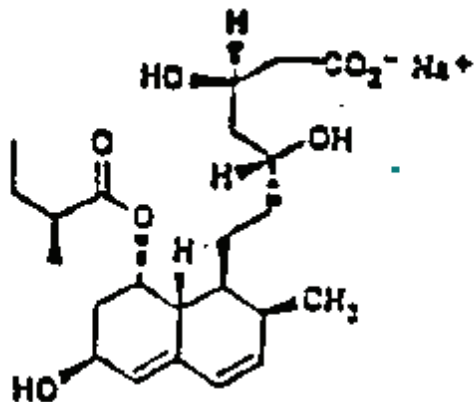## PHARMACEUTICAL INFORMATION

pal-Pravastatin

Drug Substance

Proper Name: Pravastatin Sodium

Chemical Name:

Pravastatin sodium is designated chemically as [1S-[1α(βS*,δS*)2α,6α,8β(R*),8aα]]-1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthaleneheptanoic acid, monosodium salt.

Empirical Formula: $C_{23} H_{35} O_7 \cdot Na$

Structural Formula:

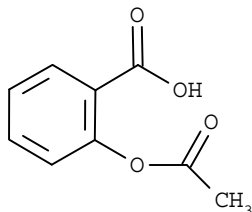Molecular Weight: 446.52

Description: Pravastatin is a white to off white, hygroscopic crystalline powder that is soluble in water, in methanol, ethanol, slightly soluble in iso-propyl alcohol and practically insoluble in acetone, acetonitrile, chloroform, ethyl-acetate and ether.

pal-ASA EC

Drug Substance

Proper Name: Acetylsalicylic acid
Chemical Names: 2-(Acetyloxy) benzoic acid; Salicylic acid acetate.

Structure:

Molecular Formula: $C_9H_8O_4$

Molecular Weight: 180.16

Description: White granules, commonly tabular or needle-like, or white crystalline powder. Odourless or having a faint odour.

Solubility: Slightly soluble in water; freely soluble in alcohol; soluble in chloroform and ether; sparingly soluble in absolute ether.

pK value (25°C):   3.49

Melting Point: 135°C (rapid heating)

CLINICAL TRIALS

pal-Pravastatin

Hypercholesterolemia
Pravastatin sodium is highly effective in reducing total and LDL cholesterol in patients with primary hypercholesterolemia. A marked response is seen within one week, and the maximum therapeutic response usually occurs within four weeks. The response is maintained during extended periods of therapy. In addition, pravastatin is effective in reducing the progressive cause of atherosclerosis and risk of coronary events, decreasing total mortality, decreasing death due to coronary heart disease, and decreasing the incidence of stroke, in hypercholesterolemic patients with atherosclerotic cardiovascular disease. Pravastatin is also effective in reducing the risk of CHD death (fatal MI and sudden death) plus non-fatal MI with no increase in deaths from non-cardiovascular causes in hypercholesterolemic patients without previous myocardial infarction. Risk reduction is evident within 6 months of the initiation of treatment (see Figure 1).

Single daily doses of pravastatin are effective. As shown in the table which follows, the Total-C and LDL-C lowering effects are the same whether pravastatin is administered in single or divided (bid) doses. Once-daily administration in the evening appears to be marginally more effective than once-daily administration in the morning, perhaps because hepatic cholesterol is synthesized mainly at night.

The results of a multicentre, double-blind regimen response comparative study of placebo and pravastatin, given to parallel groups of patients for 8 weeks are as follows:

TABLE 4

Single-daily Versus Twice-daily Dosing*

Pravastatin	N	Total-C	LDL-C	HDL-C	TG
40 mg qam	41	- 23%	- 30%	+ 4%	- 11%
40 mg qpm	33	- 26%	- 33%	+ 8%	- 24%
20 mg bid	44	- 27%	- 34%	+ 8%	- 25%

*   Evening doses were administered at least 3 hours after the evening meal. Morning doses were administered at least 1 hour prior to breakfast.
        Patients with primary hypercholesterolemia (71% Familial or Familial Combined, 29% Non-Familial).
        Baseline mean LDL-C = 6.34 mmol/L (245.4 mg/dL)

In multicentre, double-blind studies of patients with primary hypercholesterolemia, pravastatin administered in daily doses ranging from 5 mg to 80 mg to over 1100 patients was compared

with placebo. Pravastatin significantly decreased Total-C and LDL-C levels, and Total-C/HDL-C and LDL-C/HDL-C ratios. In addition, pravastatin slightly increased HDL-C and decreased VLDL-C and plasma TG levels.

Dose-response effects on lipids from two studies evaluated after 8 weeks of administering pravastatin once or twice-daily are illustrated in the tables below.

TABLE 5

Dose-response Results*

(Once-Daily Administration at Bedtime)

Pravastatin	N	Total-C	LDL-C	HDL-C	TG
5 mg qd	16	- 14%	- 19%	+ 5%	- 14%
10 mg qd	18	- 16%	- 22%	+ 7%	- 15%
20 mg qd	19	- 24%	- 32%	+ 2%	- 11%
40 mg qd	18	- 25%	- 34%	+ 12%	- 24%

*   Patients with primary hypercholesterolemia (28% Familial or Familial Combined, 72% Non-Familial).
        Baseline mean LDL-C = 5.68 mmol/L (219.6 mg/dL)

TABLE 6

Dose-response Results *

(BID Administration)

Pravastatin	N	Total-C	LDL-C	HDL-C	TG
5 mg bid	59	- 15%	- 20%	+ 7%	- 14%
10 mg bid	53	- 18%	- 24%	+ 6%	- 17%
20 mg bid	56	- 24%	- 31%	+ 5%	- 17%

*   Patients with primary hypercholesterolemia (70% Familial or Familial Combined, 30% Non-Familial).
        Baseline mean LDL-C = 6.06 mmol/L (234.5 mg/dL)

Pravastatin is also effective when given with a bile acid-binding resin. In a study of pravastatin administered alone or in combination with cholestyramine, marked reductions in the level of LDL-C were observed. In addition, pravastatin attenuated the increase in TG levels observed

with cholestyramine alone. (The results of the study cited in the table which follows should be interpreted in the context of the exceptionally high rate of patient compliance with the bile acid-binding resin [70% of patients were taking 20 or 24 g daily].)

TABLE 7

Comparison With Cholestyramine Resin*

	N	Total-C	LDL-C	HDL-C	TG
Pravastatin					
20 mg bid	49	- 24%	- 32%	+ 6%	- 10%
40 mg bid	52	- 30%	- 39%	+ 5%	- 15%
Resin Alone**	41	- 22%	- 31%	+ 2%	+ 16%
Combination					
20 mg bid & Resin**	49	- 38%	- 52%	+ 5%	- 1%

*   Patients with primary hypercholesterolemia (68% Familial or Familial Combined; 32% Non-Familial). Baseline mean LDL-C = 6.09 mmol/L (235.3 mg/dL)
**   The dose of resin used in this study was 24 g.

Primary Prevention of Coronary Events

Pravastatin has been shown to be effective in reducing the risk of coronary heart disease (CHD) death plus non-fatal MI in hypercholesterolemic patients without previous myocardial infarction.

In the West of Scotland Study (WOS), the effect of pravastatin on fatal and non-fatal coronary heart disease (CHD) was assessed in 6595 patients. The patient population consisted of men 45-64 years of age, without a previous MI, and with LDL-C levels between 4 - 6.7 mmol/L (156 - 254 mg/dL). In this randomized, double-blind, placebo-controlled study, patients were treated with standard care, including dietary advice, and either pravastatin 40 mg daily (n = 3302) or placebo (n = 3293) for a median duration of 4.8 years.

Pravastatin significantly reduced the risk of CHD death plus non-fatal MI by 31% (248 patients) in the placebo group [CHD death = 44, non-fatal MI = 204] vs 174 patients in the pravastatin group [CHD death = 31, non-fatal MI = 143], p = 0.0001). As shown in the figure below, divergence in the cumulative event rate curves for this endpoint begins within 6 months of treatment. This reduction was similar and significant throughout the entire range of baseline LDL cholesterol levels with a 37% risk reduction for LDL cholesterol 4 - 4.8 mmol/L (156 - 188 mg/dL) (p = 0.003) and a 27% risk reduction for LDL cholesterol 4.9 - 6.7 mmol/L (189 - 254 mg/dL) (p = 0.03). This reduction was also similar and significant for all age groups studied with a 40% risk reduction for patients younger than 55 years (p = 0.002) and 27% risk reduction for patients 55 years and older (p = 0.009).
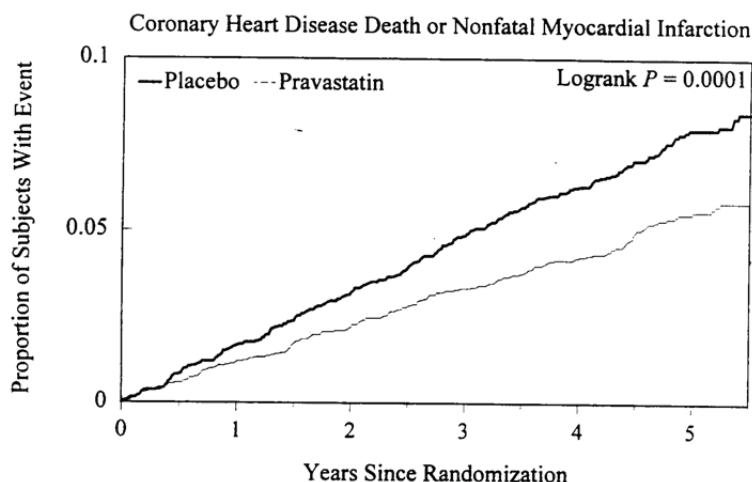
Figure 1.

Total cardiovascular deaths were reduced by 32% (73 vs 50, p = 0.03) and overall mortality by 22% (135 vs 106, p = 0.051). There was no statistically significant difference between treatment groups in non-cardiovascular mortality, including cancer deaths. Pravastatin also decreased the risk for undergoing myocardial revascularization procedures (coronary artery bypass graft surgery or coronary angioplasty) by 37% (80 vs 51 patients, p = 0.009) and coronary angiography by 31% (128 vs 90, p = 0.007).

Secondary Prevention of Cardiovascular Events

Pravastatin has been shown to be effective in reducing the risk for total mortality, CHD death, recurrent coronary events (including myocardial infarction), frequency of stroke or transient ischemic attacks (TIA), need for myocardial revascularization procedures, and need for hospitalization in patients with a history of either myocardial infarction or unstable angina pectoris.

In the **L**ong-Term **I**ntervention with **P**ravastatin in **I**schemic **D**isease (LIPID) study, the effect of pravastatin 40 mg daily was assessed in 9014 men and women with normal to elevated serum cholesterol levels (baseline Total-C=155-271 mg/dL [4.0-7.0 mmol/L]; median Total-C=218 mg/dL [5.66 mmol/L]; median LDL-C =150 mg/dL [3.88 mmol/L]), and who had experienced either a myocardial infarction or had been hospitalized for unstable angina pectoris in the preceding 3-36 months. Patients with a wide range of baseline levels of triglycerides were included (443 mg/dL [5.0 mmol/L]) and enrollment was not restricted by baseline levels of HDL cholesterol. At baseline, 82% of patients were receiving acetylsalicylic acid, 47% were receiving beta blockers, and 76% were receiving antihypertensive medication. Patients in this multicentre, double-blind, placebo-controlled study participated for a mean of 5.6 years (median=5.9 years).

Treatment with pravastatin significantly reduced the risk for CHD death by 24% (p=0.0004). The risk for coronary events (either CHD death or nonfatal MI) was significantly reduced by

31

24% (p<0.0001) in the pravastatin treated patients. The risk for fatal or nonfatal myocardial infarction was reduced by 29% (p<0.0001). Pravastatin reduced both the risk for total mortality by 23% (p<0.0001) and cardiovascular mortality by 25% (p<0.0001) . The risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) was significantly reduced by 20% (p<0.0001) in the pravastatin treated patients. Pravastatin also significantly reduced the risk for stroke by 19% (p=0.0477). Treatment with pravastatin significantly reduced the number of days of hospitalization per 100 person-years of follow-up by 15% (p<0.001). The effect of pravastatin on reducing CHD events was consistent regardless of age, gender, or diabetic status. Among patients who qualified with a history of myocardial infarction, pravastatin significantly reduced the risk for total mortality and for fatal or non-fatal MI (risk reduction for total mortality = 21%, p = 0.0016; risk reduction for fatal or non-fatal MI = 25%, p = 0.0008). Among patients who qualified with a history of hospitalization for unstable angina pectoris, pravastatin significantly reduced the risk for total mortality and for fatal or non-fatal MI (risk reduction for total mortality = 26%, p = 0.0035; risk reduction for fatal or non-fatal MI = 37%, p = 0.0003).

In the Cholesterol and Recurrent Events (CARE) study the effect of pravastatin 40 mg daily on coronary heart disease death and nonfatal MI was assessed in 4159 men and women with normal serum cholesterol levels (baseline mean Total-C=209 mg/dL [5.4 mmol/L]), and who had experienced a myocardial infarction in the preceding 3-20 months. At baseline, 83% of patients were receiving acetylsalicylic acid, 55% had undergone PTCA/CABG, 40% were receiving beta blockers, and 82% were receiving antihypertensive medication. Patients in this double-blind, placebo-controlled study participated for an average of 4.9 years. Treatment with pravastatin significantly reduced the rate of a recurrent coronary event (either CHD death or nonfatal MI) by 24% (274 patients with events [13.3%] in the placebo group vs. 212 patients [10.4%] in the pravastatin group, p=0.003). The reduction in risk for this combined endpoint was significant for both men and women; in women, the reduction in risk was 43% (p=0.033). The risk of undergoing revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) was significantly reduced by 27% (p<0.001) in the pravastatin treated patients (391 [19.6%] vs 294 [14.2%] patients). Pravastatin also significantly reduced the risk for stroke by 32% (p=0.032), and stroke or transient ischemic attack (TIA) combined by 26% (124 [6.3%] vs 93 [4.7%] patients, p=0.025).

Atherosclerotic Disease Progression

In two controlled trials [PLAC I, PLAC II] in patients with moderate hypercholesterolemia and atherosclerotic cardiovascular disease, pravastatin was effective in reducing the progressive course of atherosclerosis as evaluated by quantitative angiography and B-mode ultrasound. This effect may be associated with an improvement in the coronary endpoints (fatal or non fatal MI). No difference in total mortality was detected during the 3 years of double-blind therapy.

In PLAC I (Pravastatin Limitation of Atherosclerosis in the Coronary Arteries), a 3-year, placebo-controlled, multicentre, randomized trial, of 408 patients with moderate hypercholesterolemia (baseline LDL-C range = 3.37 - 4.92 mmol/L (130-190 mg/dL)) and coronary artery disease, treatment with pravastatin reduced the rate of narrowing of the coronary

artery lumen diameter as determined by quantitative angiography. The analyses of clinical cardiovascular events showed a favorable effect of pravastatin therapy on events that occurred > 90 days after randomization, as well as for events from the time of randomization. This effect was not accompanied by an improvement in the total mortality endpoint. In PLAC II (Pravastatin Lipids and Atherosclerosis in the Carotid Arteries), a 3-year, placebo-controlled trial, in 151 patients with moderate hypercholesterolemia (baseline LDL-C range = 3.76 - 4.92 mmol/L (145-190 mg/dL)) and coronary and carotid atherosclerosis, treatment with pravastatin significantly reduced the rate of progression of atherosclerosis in common carotid artery, as measured by B-mode ultrasound. The rate of progression of the mean-maximum intimal-medial thickness (IMT) was not significantly reduced. There was a decrease in the incidence of coronary events of borderline significance. No difference in total mortality was observed during the 3 years of double-blind therapy.

Solid Organ Transplant

Myopathy has not been observed in clinical trials involving a total of 100 post-transplant patients (76 cardiac and 24 renal) treated concurrently for two years with pravastatin (10 - 40 mg) and cyclosporine some of whom also received other immunosuppressants. Further, in clinical trials involving small numbers of patients treated with pravastatin, together with niacin, there were no reports of myopathy.

pal-ASA EC

Anti-inflammatory effect:
Components of the anti-inflammatory action of the salicylates are increased capillary resistance, thus reducing capillary leakage in response to local toxins, interference with the production of tissue-destructive lysosomal enzymes and inhibition of the synthesis of prostaglandin E compounds which have been shown to be potent mediators of the inflammatory process. Besides interfering with the synthesis of prostaglandins ASA also acts by interfering with lymphocyte activation and lymphokine production. Lymphokines are produced by activated thymus lymphocytes, which are abundant in the inflammatory tissues of patients suffering from rheumatoid arthritis. They cause increased vascular permeability and white blood cell chemotaxis, activate macrophages and stimulate lymphocyte DNA synthesis. They also induce release of tissue-destructive lysosomal enzymes as well as prostaglandins. The prostaglandins themselves, beside causing many manifestations of inflammation also act as a potent negative feedback mechanism by inhibiting lymphokine production. An indepth review of the effects of ASA on the lymphocyte-macrophage axis in inflammation has recently been published.

Effects on platelets: relation to hemostasis and thrombosis:

Platelets play an important role in normal hemostasis and clinical pathologic and experimental evidence indicates that their aggregation may play an equally important role in the evolution of a variety of disease states including cerebrovascular disease, ischemic heart disease and

myocardial infarction. pal-ASA EC inhibits platelet aggregation by irreversibly acetylating platelet cyclo-oxygenase, thereby blocking the production of prostaglandin endoperoxides PGG_2 and PGH_2 which are precursors of the major platelet-aggregating material, thromboxane A_2, which is also a powerful vasoconstrictor. However, pal-ASA EC does not prevent the adherence of platelets to damaged vessel walls or the release of granule contents from these adherent platelets. As the anuclear platelets are unable to synthesize new enzyme molecules to replace those that have been inactivated, inhibition of platelet aggregation by pal-ASA EC thus persist for the life of the platelets.

Daily administration of 20 to 40 mg of ASA to healthy volunteers reduced platelet thromboxane production, but inhibited platelet aggregation only partially. When administered to patients recovering from myocardial infarction, 50 mg ASA daily had the same effects on thromboxane production, platelet aggregation and bleeding times as 324 mg ASA daily. Other studies show that ASA doses of 40 to 325 mg daily suppressed thromboxane production by at least 80 %, but 80 mg ASA daily was the lowest dose required for maximum cumulative thrombocyte function inhibition. The protective effect of ASA against experimentally induced thrombosis or atherosclerosis has been demonstrated in several animal models.

Besides inhibiting the biosynthesis of thromboxane A_2 by platelets, ASA also interferes with the production of prostacyclin (PGI_2) by vascular endothelial cells, the above-mentioned prostaglandin endoperoxides being common precursors of both thromboxane A_2 and prostacyclin. This latter compound is one of the most powerfully acting platelet deaggregators and vasodilators and thus it would appear that the interference with the hemostatic processes by ASA depends on the thromboxane-prostacyclin balance. In fact, it has been suggested that under some conditions, high doses of ASA may be thrombogenic. However, in contrast to platelets, the vascular endothelial cells are able to regenerate cyclo-oxygenase in a relatively short time and therefore therapeutic doses of ASA are likely to produce a lesser inhibition of the vascular prostacyclin system than of the platelet thromboxane-forming mechanism. In fact, there is no clinical evidence to indicate that high doses of ASA would result in an increased risk of thromboembolism. Indeed, quite the contrary was observed and , in a controlled study, paradoxical shortening of the bleeding time was not observed at a daily ASA dose of 3.6 g. Lower dosages of ASA make selective blocking of the TxA_2-synthesis without a simultaneous blocking of PGI_2-production possible.

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The effect of time to therapy revealed that patients treated with ASA "early" (0 to 4 hours) versus "late" (5 to 24 hours) after symptom onset experienced reductions in the odds of vascular death of 25% and 21% compared with placebo at 5 weeks. 'Early' treatment with ASA resulted in the saving of 4 additional lives per 1000 patients versus 'late' treatment.

Long term follow-up (up to 10 years) of patients in this study established that the early survival advantage to ASA persisted long term, and that this prolonged benefit was additive to that of fibrinolytic therapy.

The use of ASA for secondary prevention of thrombotic events is supported by a comprehensive overview of a number of clinical trials involving patients who already had some type of vascular disease (myocardial infarction, unstable angina, stroke or transient cerebral ischemia). Overall, these studies point to a 26-28% reduction of the combined endpoints of MI, stroke, or vascular deaths by treatment with ASA alone at doses of 75 to 325 mg daily. Studies which directly compared low doses with higher doses (30-1200 mg/day), indicated that the incidence of gastrointestinal adverse effects were significantly less common with the lower doses.

Recent discussions have focused on the efficacy of ASA for the primary prevention of myocardial infarction and stroke. Two large scale randomized trials, aimed at evaluating prophylactic use of ASA, were conducted among apparently healthy male physicians (22,000 in the United States and 5,000 in the United Kingdom) respectively and their results have been published. In the summary overview of the combined results presented by the principal investigators, the authors state that: ".....Taken together, these two primary-prevention studies demonstrate a significant (P<0.0001) reduction in non-fatal myocardial infarction of about one third."

On the other hand, the same two studies have not indicated any reduction in overall vascular mortality and also suggested a slight increase in the risk of non-fatal disabling stroke. Current controversy exists about the applicability of these findings, obtained in a selected population, to the general public. As well, the optimum dosage regimen still remains an open question in this regard. Thus, the use of ASA for primary prevention should remain, in the words of the principal investigators:

"A matter of judgment in which the physician considers the cardiovascular risk profile of the patient and balances the known hazards of acetylsalicylic acid...against the clearly established reduction in the incidence of a first myocardial infarction."

DETAILED PHARMACOLOGY

pal-Pravastatin

In both normal volunteers and patients with hypercholesterolemia, treatment with pravastatin reduced total-C, LDL-C, apolipoprotein B, VLDL-C and TG while increasing HDL-C and apolipoprotein A. The mechanism of action of pravastatin is complex. Inhibition of hepatic VLDL synthesis and/or secretion occurs, leading to a decrease in LDL precursor formation. The reduction in hepatic cellular pools of cholesterol, resulting from the specific and reversible inhibition of HMG-CoA reductase activity, leads to an increase in the fractional catabolic rate of IDL and LDL via increased expression of LDL receptors on the surface of hepatic cells. Through a combination of these and possibly other unknown metabolic effects, a decline in the serum level of cholesterol results.

Pharmacokinetics

Pravastatin sodium is administered orally in the active form. Following oral ingestion, pravastatin is rapidly absorbed with peak plasma levels attained at about 1 to 1.5 hours. Average oral absorption of pravastatin, based on urinary recovery of radiolabelled drug after oral and intravenous dosing, is 34%; average absolute bioavailability of the parent drug is 17%. The therapeutic response to pravastatin is similar, whether taken with meals or one hour prior to meals, even though the presence of food in the gastrointestinal tract causes a reduction in systemic bioavailability.

TABLE 8

Percent Decrease in LDL-C

Pravastatin	10 mg bid	20 mg bid
With meals	- 25%	- 37%
Before meals *	- 26%	- 36%

* administered one hour or more prior to eating.

Pravastatin undergoes extensive first pass extraction in the liver (estimated hepatic extraction ratio, 66%), its primary site of action, and is excreted in the bile. Therefore, plasma levels of the drug are probably of limited value in predicting therapeutic effectiveness. Nevertheless, measurement of plasma pravastatin concentrations by gas chromatography and mass-spectrometry showed dose proportionality for area under the concentration-time curve (AUC) and maximum and steady-state plasma levels. Steady-state areas under the plasma

concentration-time-curves and maximum (Cmax) or minimum (Cmin) plasma concentrations showed no accumulation following once or twice-daily administration of pravastatin tablets.

Protein binding of pravastatin is approximately 50%. The plasma elimination half-life of pravastatin is between 1.5 and 2 hours (2.5 to 3 hours in hypercholesterolemic subjects). Approximately 20% of a radiolabelled oral dose is excreted in the urine and 70% in the feces. Pravastatin is extensively metabolized. The major metabolite is the 3-hydroxy isomer, which has one-tenth to one-fortieth of the inhibitory activity of the parent compound on HMG-CoA reductase.

After intravenous administration to healthy subjects, approximately 47% of the total drug clearance occurs via renal excretion of intact pravastatin, and about 53% is cleared by non-renal routes, i.e. biliary excretion and biotransformation.

Studies of pravastatin administered as a single dose to healthy elderly male and female subjects (age 65 to 78 years) indicated a 30 - 50% increase in plasma levels.

No studies have been carried out in patients with renal insufficiency.

pal-ASA EC

Absorption, distribution, metabolism and excretion:

When ASA is taken orally, it is rapidly absorbed from the stomach and proximal small intestine. The gastric mucosa is permeable to the non-ionized form of acetylsalicylic acid, which passes through the stomach wall by a passive diffusion process.

Optimum absorption of salicylate in the human stomach occurs in the pH range of 2.15 to 4.10. Absorption in the small intestine occurs at a significantly faster rate than in the stomach. After an oral dose of 0.65 g ASA, the plasma acetylsalicylate concentration in man usually reaches a level between 0.6 and 1.0 mg % in 20 minutes after ingestion and drops to 0.2 mg % within an hour. Within the same period of time, half or more of the ingested dose is hydrolyzed to salicylic acid by esterases in the gastrointestinal mucosa and the liver, the total plasma salicylate concentration reaching a peak between one or two hours after ingestion, averaging between 3 and 7 mg %. Many factors influence the speed of absorption of ASA in a particular individual at a given time; tablet disintegration, solubility, particle size, gastric emptying time, psychological state, physical condition, nature and quantity of gastric contents, etc., all affect absorption.

Distribution of salicylate throughout most body fluids and tissues proceeds at a rapid rate after absorption. Aside from the plasma itself, fluids which have been found to contain substantial amounts of salicylate after oral ingestion include spinal, peritoneal and synovial fluids, saliva and milk. Tissues containing high concentrations of the drug are the kidney, liver, heart and lungs. Concentrations in the brain are usually low, and are minimal in feces, bile and sweat.

The drug readily crosses the placental barrier. At clinical concentrations, from 50% to 90% of the salicylate is bound to plasma proteins especially albumin, while acetylsalicylic acid itself is bound to only a very limited extent. However, ASA has the capacity of acetylating various proteins, hormones, DNA, platelets and hemoglobin, which at least partly explains its wide ranging pharmacological actions.

The liver appears to be the principal site for salicylate metabolism, although other tissues may also be involved. The three chief metabolic products of ASA or salicylic acid are salicyluric acid, the ether or phenolic glucuronide and the ester or acyl glucuronide. A small fraction is also converted to gentisic acid and other hydroxybenzoic acids. The half-life of ASA in the circulation is from 13 to 19 minutes so that the blood level drops quickly after absorption is complete. However, the half-life of the salicylate ranges between 3.5 and 4.5 hours, which means that 50% of the ingested dose leaves the circulation within that time.

Excretion of salicylates occurs principally via the kidney, through a combination of glomerular filtration and tubular excretion, in the form of free salicylic acid, salicyluric acid, as well as phenolic and acyl glucuronides. Salicylate can be detected in the urine shortly after its ingestion, but the full dose requires up to 48 hours for complete elimination. The rate of excretion of free salicylate is extremely variable, reported recovery rates in human urine ranging from 10% to 85%, depending largely on urinary pH. In general, it can be stated that acid urine facilitates reabsorption of salicylate by renal tubules, while alkaline urine promotes excretion of the drug.

Anti-inflammatory effect:

Components of the anti-inflammatory action of the salicylates are increased capillary resistance, thus reducing capillary leakage in response to local toxins, interference with the production of tissue-destructive lysosomal enzymes and inhibition of the synthesis of prostaglandin E compounds which have been shown to be potent mediators of the inflammatory process. Besides interfering with the synthesis of prostaglandins, ASA also acts by interfering with lymphocyte activation and lymphokine production. Lymphokines are produced by activated thymus lymphocytes, which are abundant in the inflammatory tissues of patients suffering from rheumatoid arthritis. They cause increased vascular permeability and white blood cell chemotaxis, activate macrophages and stimulate lymphocyte DNA synthesis. They also induce release of tissue-destructive lysosomal enzymes as well as prostaglandins. The prostaglandins themselves, beside causing many manifestations of inflammation, also act as a potent negative feedback mechanism by inhibiting lymphokine production. An indepth review of the effects of ASA on the lymphocyte-macrophage axis in inflammation has recently been published.

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"A matter of judgment in which the physician considers the cardiovascular risk profile of the patient and balances the known hazards of aspirin...against the clearly established reduction in the incidence of a first myocardial infarction."

Animal Pharmacology

The pre-clinical studies discussed below were not performed on the product combination but on each individual product under specific laboratory conditions.

pal-Pravastatin

Cell/Tissue Selective Inhibition of Cholesterol Synthesis

In vitro and animal studies have shown that pravastatin, a hydrophilic HMG-CoA reductase inhibitor, is tissue selective such that inhibitory activity is highest in those tissues with the highest rates of cholesterol synthesis, such as the liver and ileum.

In suspensions of freshly isolated rat hepatocytes and in one-day cultures of rat hepatocytes, pravastatin sodium showed potent inhibition of ^{14}C incorporation into cholesterol. In cultured human skin fibroblasts and other non hepatic cell types, pravastatin inhibited cholesterol synthesis 400 times less than in hepatocytes.

The accumulation of ^{14}C-pravastatin was concentration and time-dependent in hepatocytes and barely detectable in fibroblasts.

In tissue slices from rats given oral doses of pravastatin sodium, cholesterol synthesis was inhibited by more than 90% in liver and ileum slices and was substantially lower or not detectable in other tissue slices such as prostate, testes and adrenal.

In the intact rat lens, pravastatin sodium inhibited cholesterol synthesis 10 times less than in liver from the same animals. The inhibition of sterol synthesis in lens epithelial lines derived from the mouse and the rabbit was 400 to 1500 times less than in rat hepatocytes.

Specificity as an Inhibitor of HMG-CoA Reductase

The incorporation of ^{14}C-mevalonate, the product of HMG-CoA reductase reaction into sterols, was not affected in hepatocytes, fibroblasts, or CHO cells at concentrations of pravastatin sodium at least 20 times greater than those that inhibited ^{14}C-acetate incorporation into cholesterol.

At concentrations 500 times greater than those that inhibited acetate incorporation into cholesterol, pravastatin sodium did not alter the rate of incorporation of ^{14}C-acetate into total cell phospholipids in hepatocytes and the distribution of the radiolabel into the separate classes of phospholipids. Pravastatin sodium did not reduce the rate of incorporation of ^{14}C-acetate into triglycerides. These results demonstrate that pravastatin does not act in the sterol pathway at any step beyond the synthesis of mevalonate, nor does it inhibit the enzymes required for the biosynthesis of two other major classes of lipids.

The inhibitory activity of pravastatin on the enzyme HMG-CoA reductase was 106 times greater than that demonstrated by pravastatin for HMG-CoA lyase. The active site of this enzyme, which also employs HMG-CoA as substrate, does not recognize pravastatin.

General pharmacology

The effect of pravastatin sodium on major physiologic systems and isolated tissue and its agonist and antagonist effects towards principal neurohumoral transmitters or histamine, behavioural effects, convulsive threshold and tissue- or activity-specific effects were evaluated in animals or *in vitro* tissue preparations. With the exception of a moderate inhibition of gastric secretion at a dose of 300 mg/kg in rats, pravastatin sodium had no effect in any of these pharmacologic tests at doses of 1000 mg/kg in some species.

Pharmacokinetics

Studies in rats, dogs and humans demonstrated that pravastatin sodium given orally has low bioavailability because of extensive first-pass hepatic extraction. Therefore, most of an oral dose of pravastatin sodium is delivered directly to the liver, the primary site of pharmacologic activity.

A relatively low extent of binding of pravastatin to plasma proteins was found in rats, dogs, monkeys and humans. The highest concentrations of ^{14}C-pravastatin were found in the excretory organs and the GI tract in rats (N=3-5), one dog and one monkey. Similar metabolic patterns and appreciable fecal excretion in rats, dogs, monkeys and humankind were also evident in these studies.

Dogs are unique as compared to all other species tested, including humankind, in that they have a much greater systemic exposure to pravastatin. Pharmacokinetic data from a study in dogs at a dose of 1.1 mg/kg (comparable to a 40 mg dose in humans) showed that the elimination of pravastatin is slower in dogs than in humans. Absolute bioavailability is two times greater in dogs compared to humans and estimated renal and hepatic extraction of pravastatin are about one-tenth and one-half, respectively, than those in humans. When concentrations of pravastatin in plasma or serum of rats, dogs, rabbits, monkeys and humans were compared, the exposure in dogs was dramatically higher, based on both C_{max} and AUC. The mean AUC value in humankind at a therapeutic dose of 40 mg is approximately 100 times less than that in the dog at the no-effect dose of 12.5 mg/kg, and approximately 180 times lower than that in dogs at the threshold dose of 25 mg/kg for cerebral hemorrhage.

Placental Transfer

Low levels of radioactivity were found in the fetuses of rats dosed orally with radiolabelled pravastatin sodium. Pravastatin sodium was also found to be secreted in the milk of rats.

TOXICOLOGY

The toxicology studies discussed below were not performed on the product combination but on each individual product under specific laboratory conditions.

pal-Pravastatin

Acute Toxicity

TABLE 9

Species	Sex (N)	Route	LD50 (mg/kg)
Mouse	M (50) F (50)	Oral	10590 8939
Mouse	M (50) F (50)	i.v.	2114 2011
Mouse	M (50) F (50)	s.c.	2975 3667
Rat	M (20) F (20)	Oral	> 12000 > 12000
Rat	M (50) F (50)	i.v.	443 440
Rat	M (50) F (50)	s.c.	3172 4455
Dog	M (4)	Oral	> 800

Signs of toxicity in mice were decreased activity, irregular respiration, ptosis, lacrimation, soft stool, diarrhea, urine-stained abdomen, ataxia, creeping behavior, loss of righting reflex, hypothermia, urinary incontinence, pilo-erection convulsion and/or prostration.

Signs of toxicity in rats were soft stool, diarrhea, decreased activity, irregular respiration, waddling gait, ataxia, loss of righting reflex and/or weight loss.

Subacute and Chronic Toxicity

The spectrum of effects produced by pravastatin in mice, rats, rabbits, dogs and monkeys shown on the following table is not unexpected in view of the magnitude of the dosage levels employed and the potency of pravastatin against the HMG-CoA reductase.

TABLE 10

Target Organs Observed in Animal Studies

Organ	Mouse	Rat	Rabbit	Dog	Monkey
Liver, neoplastic effect	~	+	~	~	~
Liver, non-neoplastic effect	+	+	+	~	+
Kidney	~	~	+	~	+
Skeletal muscle	~	+	+	~	~
Brain	~	~	~	+	~

+ = Organ affected in some way by drug treatment
- = No effect observed in this organ in these species

On a mg/kg basis, rabbits appear to be more sensitive to the nephrotoxic effects of pravastatin sodium than monkeys, the only other species that exhibited renal toxicity. In rabbits, renal dysfunction and hepatic effects were observed at doses $\geq$ 25 mg/kg/day. In monkeys, hepatotoxicity and nephrotoxicity occurred at doses of 100 mg/kg/day. The threshold dose for renal toxicity in rabbits is 31 times greater than the maximum human dose.

TABLE 11

Significant Adverse Changes

	Pravastatin	
	MINIMAL TOXIC DOSE (mg/kg/day)	**NO-EFFECT DOSE** (mg/kg/day)
Mice		
Single-cell necrosis in the liver	40	20
Elevated serum transaminase activity	20	10
Rats		
Hepatic tumors	100	40
Foci of hepato-cellular alteration	30	12
Elevated transaminase activity	100	50
Skeletal-muscle myolysis	400	250
Rabbits		
Death	400	100
Hepatocellular necrosis	100	25
Renal tubular degeneration	25	6.25
Skeletal-muscle myolysis	100	25
Elevated serum transaminase activity	100	25
Dogs		
Death	25	12.5
Cerebral hemorrhage	25	12.5
Monkeys		
Death	200	100
Hepatocellular necrosis	100	50
Renal tubular degeneration	100	50
Elevated serum transaminase activity	100	50

Noteworthy findings in these studies included varying degrees of hepatotoxicity in all species tested, renal toxicity in rabbits and monkeys, skeletal-muscle lesions in rabbits, CNS symptoms and death secondary to cerebral hemorrhage in dogs, and an increased incidence of hepatic lesions and evidence of hepatocarcinoma (the latter at 100 mg/kg) in rats treated for 2 years. In all cases, these changes occurred only at daily doses of 20 mg/kg or more (more than 25 times the maximum human dose).

The findings from the chronic toxicity in dogs are detailed on the following pages.

TABLE 12

Species/ Strain	Sex	N/Dose	Dose (mg/kg/day)	Route	Time	Effects
Subacute Toxicity						
Dog Beagle	M F	33	0, 12.5, 50 or 200	Oral (capsule)	5 weeks	200 mg/kg: One dog died and 4 dogs sacrificed on days 11 to 22 after exhibiting ataxia and/or convulsions, salivation, urinary incontinence and/or defecation. Ecchymotic lesions (hemorrhagic foci) in the brain.
Dog Beagle	M F	66	0 or 100 (2M, 2F controls) (4M, 4F treated)	Oral (capsule)	13 weeks	100 mg/kg: One death (F) on day 42 preceded by marked decrease in activity, serous salivation and vomiting. Diapedetic hemorrhage and degeneration of venular endothelial cells in one F and the F that died.

Chronic Toxicity						
Dog Beagle	M F	4M, 4F at 12.5 and 25 - 6M, 6F at 0, 50 & 100	0, 12.5, 25, 50 or 100	Oral (capsule)	2 years	25 mg/kg: Two F sacrificed during weeks 60 and 61. One had lesions consistent with idiopathic coagulopathy. The other showed clinical signs of CNS toxicity prior to sacrifice and had brain lesions.[1] 50 mg/kg: All dogs showed clinical signs of CNS toxicity; 5/6 dogs had brain lesions.[1] 100 mg/kg: Three M and 5 F died or sacrificed between weeks 2 and 24. One M died in week 76. All dogs showed clinical signs of CNS toxicity prior to death/sacrifice. Nine/nine dogs had brain lesions.

1 Brain lesions (primarily in the piriform lobes) were characterized by discrete multifocal perivascular capilary and venular hemorrhages. In more sever lesions, there was an increased number of focal perivascular hemorrhages and associated early degenerative neutrophil changes including vacuolization, edema, and mild neutrophil infiltration. Larger vascular elements were not involved. No vascular endothelial changes were present, based on light- and electron-microscopic studies.

In dogs, pravastatin sodium was toxic at high doses and caused cerebral hemorrhage with clinical evidence of acute CNS toxicity (e.g. ataxia, convulsions). A dose-response relationship with respect to the incidence of CNS toxicity was clearly evident. In dogs, the threshold dose for CNS toxicity is 25 mg/kg. The high systemic exposure to orally administered pravastatin in dogs (refer to **DETAILED PHARMACOLOGY**, Pharmacokinetics) may be related to a greater bioavailability and slower elimination of pravastatin and likely plays an important role in the development of CNS lesions that occur in the dog.

Cerebral hemorrhages have not been observed to date in any other laboratory species and the CNS toxicity in dogs may represent a species-specific effect.

Reproduction and Teratology

Aside from a slight maternal toxicity in rabbits at 50 mg/kg and in rats at 1000 mg/kg, there were no treatment-related findings.

In rabbits and rats at doses greater than 60 and 600 times respectively the maximum human dose, pravastatin sodium exerted no untoward effects on reproduction through the F_1 generation in rats and did not cause any fetal or anatomic abnormalities through the F_1 generation in rabbits and the F_2 generation rats.

Carcinogenicity and Mutagenicity

In mice and rats, treated for 21 months with oral doses 25 and 50 times the maximum human dose respectively (i.e. 20 mg/kg daily and 40 mg/kg daily), pravastatin sodium was found to be non carcinogenic. After 86 and 104 weeks of dosing in mice and rats respectively, at oral doses 125 times the maximum human dose (i.e. 100 mg/kg daily), statistically significant increases in the incidence of hepatocellular carcinoma were observed in male rats only.

In *in vivo* mutagenicity tests with i.p. doses up to 1400 mg/kg and in *in vitro* mutagenicity tests at concentrations up to 10000 ug/mL or plate, pravastatin sodium was found to be nonmutagenic.

Pravastatin was found to be non-genotoxic.

<div align="center">

pal-ASA EC

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The clinical and pathological signs of poisoning from toxic and lethal oral doses of ASA have been extensively described for humankind, much less extensively for other species.

The <u>acute toxicity</u> of ASA in animals has been studied and reviewed in detail by Boyd. The signs of poisoning in rats from doses in the lethal range are due to varying degrees of gastroenteritis, hepatitis, nephritis, pulmonary edema, encephalopathy, shock and minor toxic effects on other organs and tissues. Death is due to convulsions or cardiovascular shock. The major difference between species appears to be the ability to vomit toxic doses seen in humankind, cats and dogs, but not in mice, rats and rabbits. Otherwise, the pathological reaction to toxic doses of ASA is similar in all species in which such studies have been reported. The acute oral LD_{50} values have been reported as being over 1.0 g/kg in humankind, cat and dog, 0.92 g/kg in female and 1.48 g/kg in male albino rats, 1.19 g/kg in guinea pig, 1.1 g/kg in mouse and 1.8 g/kg in rabbit.

<u>Chronic toxicity</u> studies were reported in mice and rats. When ASA was administered at 2 to 20 times the maximum tolerated clinical dose to mice for up to one year, a dose-related deleterious effect was observed on mean survival time, number of young born and number of young raised to weaning age, no evidence of carcinogenic effect was found.

The chronic oral LD_{50} in male albino rats has been reported as 0.24g/kg/day when given for 100 days. At these daily doses, ASA produced no anorexia and no loss of body weight. It did produce polydipsia, aciduria, diuresis, drowsiness, hyperreflexia, piloeraction, rapid and deep

respiration, tachycardia, and during the second month, soft stools, epistaxis, sialorrhea, dacryorrhea and death in hypothermic coma. Autopsy disclosed the presence of a hypertrophied stomach, renal congestion, mild hepatitis and pneumonitis. While teratogenic effects were noted in animals at near lethal doses, there is no evidence to indicate that ASA is teratogenic in humankind.

SELECTED BIBLIOGRAPHY

1.   Crouse JR, Byington RP, Bond MG, Espeland MA, Craven TE, Sprinkle JW, McGovern ME and Furberg CD. *Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC II)*. Am J Cardiol 1995;75:455-459.

2.   The Long-Term Intervention With Pravastatin In Ischaemic Disease (LIPID) Study Group. *Prevention of Cardiovascular Events and Death With Pravastatin In Pateints With Coronary Heart Disease and a Broad Range of Initial Cholesterol Levels*. New Engl J Med 1998;339(19):1349-1357.

3.   Pitt B, Mancini J, Ellis SG, Rosman HS, Park J and McGovern ME for the PLAC I Investigators. *Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): Reduction in Atherosclerosis Progression and Clinical Events*. JACC 1995;26(5):1133-1139.

4.   Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun C, Davis BR and Braunwald E. for the Cholesterol and Recurrent Events Trial Investigators. *The Effect of Pravastatin on Coronary Events After Myocardial Infarction In Patients With Average Cholesterol Levels*. New Engl J Med 1996;335(14):1001-1009.

5.   Product Monograph for *Aspirin*. Bayer Inc., July 26, 2004.

6.   Product Monograph for *Pravachol*. Bristol Myers Squibb Inc. April 26, 2005.

7.   Product Monograph for *ASA Suppositories, pms-ASA 325 mg Tablets, ASAPHEN 80 mg Tablets, ASAPHEN 81 mg Tablets, ASAPHEN EC 80mg Tablets, ASAPHEN EC 81 mg Tablets, ASAPHEN EC 162 mg*. Pharmascience Inc., March 17, 2004.

8.   Product Monograph for *pms-Pravastatin*. Pharmascience Inc., October 22, 2004.

9.   Product Monograph for *Entrophen*. Pharmascience Inc., October 31, 2006.

PART III: CONSUMER INFORMATION

[Pr]Pal-Pravastatin-ASA
Pravastatin sodium tablets
and
Acetylsalicylic acid delayed-release tablets USP

This leaflet is part III of a three-part "Product Monograph" published when Pal-Pravastatin-ASA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Pal-Pravastatin-ASA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Pal-Pravastatin-ASA is indicated for the patients for whom treatment with both pal-Pravastatin and pal-ASA EC at the same time is appropriate. As the two medications are co-packaged in a compliance pack, you may find Pal-Pravastatin-ASA more convenient to use.

Your doctor may prescribe a program of weight control, smoking cessation, physical exercise and/or a cholesterol-lowering diet for you while you are taking Pal-Pravastatin-ASA. Do follow your doctor's instructions.

What it does:

Pal-Pravastatin-ASA may help people who have one or more of these problems:

• a heart attack in the past
• chest pain from heart problems (also called angina)
• a bypass operation or angioplasty to open the blood vessels of the heart
• blood flow problems to the brain (such as strokes, near-strokes, or mini-strokes)

Pal-Pravastatin-ASA contains 2 medicines taken together.

pal-ASA EC stops part of the normal blood clotting process and so keeps clots or plugs from forming in your blood vessels. pal-ASA EC contains acetylsalicylic acid delayed-release and other ingredients that may lower your chance of getting an upset stomach.

pal-Pravastatin lowers your "bad" LDL cholesterol and raises your "good" HDL cholesterol. High cholesterol can lead to plugs or clots in your blood vessels.

When it should not be used:
Do not take Pal-Pravastatin-ASA if:
• you are allergic to any of the ingredients in Pal-Pravastatin-ASA.
• you are allergic to or have had breathing difficulties after using any medicines called "nonsteroidal anti-inflammatory drugs" (NSAIDs) including acetylsalicylic acid and other salicylates;
• you have an active liver disease, or unexplained, persistent elevations in liver function values (transaminases) in your blood test results;
• you have kidney problems;
• you have an active peptic ulcer;
• if you are pregnant, planning to become pregnant or breast-feeding;
• you are 18 years of age or younger.

What the medicinal ingredients are:

The active ingredient in pal-ASA EC is acetylsalicylic acid. The active ingredient in pal-Pravastatin is pravastatin sodium.

What the important non-medicinal ingredients are:

pal-Pravastatin, 10 mg, 20 mg and 40 mg.
Colloidal Silicon Dioxide, Croscarmellose Sodium, Dibasic Calcium Phosphate, Lactose Monohydrate Spray Dried, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol and Pyrrolidone/Vinyl Acetate Copolymer. Available in blister packs of 10 tablets.

pal-Pravastatin 10 mg: Iron Oxide IC07470 Red #30;
pal-Pravastatin 20 mg: Iron Oxide IC07434 Yellow #10;
pal-Pravastatin 40 mg: Lake Blend Green LB-451.

81 mg: Colloidal anhydrous silica, lactose anhydrous, methacrylic acid copolymer type C, methylated silica, methylcellulose, polyethylene glycol sorbitan tristearate, polydimethylsiloxane, pregelatinized starch, purified water, sodium bicarbonate, sodium lauryl sulphate, stearic acid, talc, titanium dioxide, triethyl citrate.

162 mg: Carnauba wax, colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose anhydrous, methylated silica, methylcellulose, polydextrose, polydimethylsiloxane, polyethylene glycol, plyvinyl aetate phthalate, pregelatinized starch , purified water, sodium alginate sodium bicarbonate, stearic acid triple presse powder, sureteric white, talc, titanium dioxide, triethyl citrate .

325 mg: Colloidal anhydrous silica, corn starch, guar gum, hydrogenated vegetable oil type I, iron oxide yellow, lecithin, methacrylic acid copolymer type C, methylated silica, methylcellulose, microcrystalline cellulose, polyethylene glycol sorbitan tristearate, polydimethylsiloxane, polyvinyl alcohol, sodium bicarbonate, sodium lauryl sulphate, talc, titanium dioxide, triethyl citrate, water.

What dosage forms it comes in:

Pal-Pravastatin-ASA contains one dosage strength of **pal-Pravastatin** (10 mg, 20 mg or 40 mg tablets) with one dosage strength of **pal-ASA EC** (81 mg, 162 mg tablets or 325 mg caplets). They are co-packaged in a compliance pack.

WARNINGS AND PRECAUTIONS

- **Pregnancy or breast feeding:**
  Pal-Pravastatin-ASA should not be used during pregnancy. Cholesterol is essential for the development of a baby. Cholesterol-lowering drugs can harm the baby. If you become pregnant while using Pal-Pravastatin-ASA, stop using the medication immediately and contact your doctor.

Pal-Pravastatin-ASA should not be used during breast feeding or if you intend to breast-feed. Pal-Pravastatin-ASA can pass into your breast milk and may harm your baby. You may need to choose between breast feeding or taking Pal-Pravastatin-ASA.

Before you use Pal-Pravastatin-ASA, talk to your doctor or pharmacist if you:

- have kidney problems
- have thyroid problems
- have bleeding problems
- have diabetes
- have severe anemia
- do excessive physical exercise
- have unexplained muscle aches or weakness, or if any occur during treatment
- have had any past problems with muscles (pain, tenderness) after using a statin
- have a personal or family history of muscular disorders
- have stomach problems such as heartburn, upset stomach, stomach pain or ulcers
- regularly drink 3 or more alcoholic drinks every day
- have asthma (wheezing) along with nasal polyps (small growths in your nose)
- are younger than 18 years; then you should not use any product with acetylsalicylic acid in it. Children can get a rare but very serious medical problem called Reye's Syndrome if they take acetylsalicylic acid when they are sick.
- have decreased liver function or active liver disease;
- are elderly.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the medicines you take, including other medicines that contain acetylsalicylic acid, prescription and non-prescription medicines, vitamin, and herbal supplements, as drug interactions are possible. You should also tell any physician who is prescribing a new medication for you that you are taking Pal-Pravastatin-ASA. Some medicines such as those listed below, can cause serious side effects if you take them while you are taking Pal-Pravastatin-ASA®. Be extra sure to tell your doctor if you take any of the following kinds of medicines:

- blood thinners. Blood thinners can increase your chance of bleeding since the acetylsalicylic acid in Pal-Pravastatin-ASA also blocks normal blood clotting.
- certain medicines for high cholesterol or high triglycerides called fibrates (gemfibrozil, fenofibrate) or niacin.
- medicines to reduce serum cholesterol ("statins") such as atorvastatin (Lipitor®), fluvastatin (Lescol®), Lovastatin (Mevacor®), pravastatin (Pravachol®), rosuvastatin (Crestor®) or simvastatin (Zocor®);
- large doses (more than 1 g/day) of niacin (nicotinic acid) (drug to lower cholesterol).

Pal-Pravastatin-ASA may affect how some of your other medicines work. If you take a high blood pressure medicine called an ACE inhibitor, you may need to have your blood pressure checked more often.

It is also important to tell your doctor if you are taking antacid, corticosteroids, methotrexate, anticoagulants (drug that prevents blood clots, such as warfarin), digoxin (a drug used to treat heart problems), ketoconazole, spironolactone, ~~or~~ cimetidine, or analgesic-antipyretic agents such as acetaminophen.

PROPER USE OF THIS MEDICATION

Pal-Pravastatin-ASA is not for initial therapy. The individual dosage of both medications within Pal-Pravastatin-ASA must be stabilized for you by your physician, before your doctor can switch you to Pal-Pravastatin-ASA.

Usual dose:

pal-Pravastatin: The recommended starting dose of pal-Pravastatin is 10 to 20 mg once daily. If the cholesterol in your blood is markedly elevated, your doctor may start you on a 40 mg/day dose.

pal-ASA EC: 1 tablet daily of 81 mg, 162 mg or 325 mg caplet as directed by your physician. Do not take more than your physician recommends. pal-ASA EC tablets have a special enteric coating designed to help prevent stomach upset. To benefit from this protection, **the tablets must be swallowed whole and should not be crushed or broken**.

The usual dose of Pal-Pravastatin-ASA is one pal-ASA EC (acetylsalicylic acid delayed release) tablet/caplet with one pal-Pravastatin (pravastatin) tablet once a day, at bedtime. Pal-Pravastatin-ASA comes in different strengths and your doctor may adjust your dose. Do not change your dose without talking to your doctor.

You need to follow your doctor's advice and take Pal-Pravastatin-ASA every day in order for it to lower your chances of dying from heart disease, having a heart attack, or having a stroke. If you stop taking Pal-Pravastatin-ASA, it will not help you anymore. You must tell your doctor if you stop taking Pal-Pravastatin-ASA.

- Take Pal-Pravastatin-ASA exactly as your doctor prescribes it.
- You can take Pal-Pravastatin-ASA with or without food.
- Take Pal-Pravastatin-ASA with a full glass of water, unless your doctor has told you to keep your fluids low.
- Your doctor will monitor your condition and have blood tests done at regular intervals. Please keep your appointments.
- Avoid excessive alcohol intake.
- Tell your doctor of any new illnesses which occur during treatment.
- Some people may need to stop taking Pal-Pravastatin-ASA completely or for a long time. Call your doctor if you plan to have any surgery, medical, or dental procedures. You may be told to stop taking Pal-Pravastatin-ASA for a while to lower your risk of bleeding.

How to use a compliance pack:
Your tablets come in press-through compliant sleeves. Your compliance pack contains 3 sleeves for a total of 30 days of therapy. Each sleeve includes 10 tablets of pal-simvastatin and 10 tablets of pal-ASA EC. Take one tablet from the orange panel and one tablet from the teal panel every day until you complete all 3 sleeves.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. Do not take 2 doses in the same day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Pal-Pravastatin-ASA can cause unwanted side effects. Possible side effects reported with some statins: breathing problems including persistent cough and/or shortness of breath or fever.

The following adverse events have been reported with some statins: Sleep Disturbances, including insomnia and nightmares. Mood related disorders including depression. Erectile dysfunction.

Check with your doctor or pharmacist promptly if any of the following persist or become troublesome:

- heartburn
- hoarseness

Call your doctor if you experience loss of hearing, including ringing or buzzing in the ears.

There is a risk of muscle breakdown for patients taking Pal-Pravastatin-ASA. The risk is greater if you are taking higher doses of Pal-Pravastatin-ASA and if you have abnormal kidney function.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		If effect persists or becomes bothersome	In all cases	
Common	Aching muscles, muscle cramps, unexplained mucle pain, tenderness, cramping, aching or weakness, rhabdomyolysis (a muscle wasting disease), associated muscle tenderness			√
	Tiredness/weakness, dizziness, fainting spells			√
	Fever	√		
	Blurred vision			√
	Constipation, diarrhea, gas, stomach upset, nausea, loss of appetite, vomiting	√		
	Pain in the abdomen/upper part of stomach	√		
	Headache	√		
	Skin rash, hives, itching	√		
Uncommon	Flushing, swelling, joint pain, fever, light sensitivity			√
	Black stools		√	
	Stomach irritation	√		
	Unusual bleeding or bruising		√	
	Brownish or discoloured urine		√	
	Liver damage: yellowing of the skin or eyes, flu-like symptoms			√
	Allergic reactions: difficulty breathing or swallowing, swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs			√

These are not all the possible side effects of Pal-Pravastatin-ASA. If other effects occur, they generally do not require medical attention, and may come and go during treatment. If any persist or become troublesome, do check with your physician or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**

    - Fax toll-free to 1-866-678-6789, or

    - Mail to :   Canada Vigilance Program

                    Health Canada

                    Postal Locator 0701D

                    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph prepared for health professionals can be obtained by contacting:

By mail:
Paladin Labs Inc.
6111 Royalmount Ave., Suite 102
Montreal, Quebec
H4P 2T4

By telephone: 1-888-550-6060
http://www.paladinlabs.com

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HOW TO STORE IT

Do not use outdated medicine.

Pal-Pravastatin-ASA is provided in a press-through compliant blister package suitable for direct distribution to the patient. Store Pal-Pravastatin-ASA in the provided package. Protect from moisture and light.

- Keep all medicines out of the reach of children.
- Store your tablets at room temperature (15-30 ºC).