PRODUCT MONOGRAPH

APO-ASA LD (LOW DOSE)

Acetylsalicylic Acid Delayed Release Tablets, USP

81 mg

Platelet Aggregation Inhibitor

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APO-ASA LD

Acetylsalicylic Acid Delayed-Release Tablets, USP

81 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Delayed Release Tablet 81 mg	Corn starch, FD&C blue # 1, hydroxypropyl methylcellulose, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, talc, titanium dioxide and triethyl citrate.

INDICATIONS AND CLINICAL USE

APO-ASA LD (acetylsalicylic acid, ASA) low dose (LD) is indicated for the following uses, based on its platelet aggregation inhibitory properties:

- for reducing the risk of vascular mortality in patients with a suspected acute myocardial infarction
- for reducing the risk of a **first** non-fatal myocardial infarction in individuals deemed to be at sufficient risk of such an event by their physician.
    - There is no evidence for a reduction in the risk of **first** fatal myocardial infarction.
    - APO-ASA LD does not reduce the risk of either cardiovascular mortality or **first** strokes, fatal or non-fatal

      The decrease in the risk of **first** non-fatal myocardial infarction, must be assessed against a much smaller but not insignificant increase in the risk of haemorrhagic stroke as well as gastrointestinal bleeding.

- for reducing the risk of morbidity and death in patients with unstable angina and in those with previous myocardial infarction
- for reducing the risk of transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction
- for prophylaxis of venous thromboembolism after total hip replacement

CONTRAINDICATIONS

- Patients who are hypersensitive to ASA, salicylates, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, antipyretics or other ingredients in the product or component of the

container. For a complete listing, see Dosage Forms, Composition and Packaging section of the product monograph.

- Acute gastrointestinal ulcer
- History of gastrointestinal ulcers
- Hemorrhagic diathesis
- Active or Severe hepatic failure, renal failure, or congestive heart failure
- Patients with a history of asthma induced by the administration of salicylates or substances with a similar action, notably NSAIDs
- Combination with methotrexate at doses of 15mg/week or more (see "Drug Interactions").
- Last trimester of pregnancy (see "Special Populations")

WARNINGS AND PRECAUTIONS

General

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

ASA should be administered cautiously to patients with:

- uncontrolled hypertension
- impaired hepatic, renal function or cardiovascular circulation (e.g. renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or major haemorrhagic events)
- a history of bleeding tendencies, significant anemia and/or hypothrombinemia
- concomitant treatment with anticoagulants (see "Drug Interactions")
- concomitant treatment with NSAIDs, such as ibuprofen and naproxen in patients on an ASA regimen (see "Drug Interactions")

Hypersensitivity

ASA may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions. Risk factors are present bronchial asthma, hay fever, nasal polyps, or chronic respiratory disease. This applies also for patients showing allergic reactions (e.g. cutaneous reactions, itching, urticaria) to other substances.

Hematologic

Due to effect on platelet aggregation, ASA may be associated with an increased risk of bleeding. Caution is necessary when salicylates and anticoagulants are prescribed concurrently, as salicylates can depress the concentration of prothrombin in the plasma.

Peri-Operative Considerations

Due to its inhibitory effect on platelet aggregation which persists for several days after administration, ASA may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g. dental extractions).

Special Populations

Women attempting to conceive:

During the first and second trimester of pregnancy, acetylsalicylic acid containing drugs should not be given unless clearly necessary. If acetylsalicylic acid containing drugs are used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low as possible and duration of treatment as short as possible.

Based on the limited published data available, the studies in humans showed no consistent effect of acetylsalicylic acid on impairment of fertility and there is no conclusive evidence from animal studies.

Pregnant Women:
Acetylsalicylic acid inhibits prostaglandin synthesis. Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of malformations after the use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. Available data do not support any association between intake of acetylsalicylic acid and an increased risk for miscarriage. For acetylsalicylic acid the available epidemiological data regarding malformation are not consistent, but an increased risk of gastroschisis could not be excluded. A prospective study with exposure in early pregnancy (1^{st} to 4^{th} month) of about 14,800 mother-child pairs has not yielded any association with an elevated rate of malformations.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus ateriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

Use of any prostaglandin synthesis inhibitors at the end of pregnancy may expose the mother and the child to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even after very low doses
- inhibition of uterine contractions resulting in delayed or prolonged labour Consequently, acetylsalicylic acid is contraindicated in the third trimester of pregnancy.

Nursing Women:
ASA and its metabolites pass into breast milk in small quantities. Since no adverse effects on the infant have been observed after occasional use, interruption of breast-feeding is usually unnecessary. However, on regular use or on intake of high doses, breast feeding should be discontinued early.

Pediatrics
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. ASA should not be used in children and teenagers for viral infections with or without

fever without consulting a physician. In certain viral illnesses, especially influenza A, influenza B and varicella, there is a risk of Reye's syndrome, a very rare but possibly life threatening illness requiring immediate medical action. The risk may be increased when ASA is given concomitantly; however, no causal relationship has been proven. Should persistent vomiting occur with such diseases; this may be a sign of Reye's syndrome.

Low Uric Acid Excretion:
At low doses, ASA reduces excretion of uric acid. This can trigger gout in patients who already tend to have low uric acid excretion.

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency:
In patient suffering from glucose-6-phosphate dehydrogenase (G6PD) deficiency, ASA may induce hemolysis or haemolytic anemia. Factors that may increase the risk of haemolysis are high dosage, fever, or acute infections.

Elderly
In general, ASA should be used with caution in elderly patients (≥ 60 years of age), as these patients may be more susceptible to adverse reactions.

Monitoring and Laboratory Tests
Salicylates can produce changes in thyroid function tests.
Isolated cases of liver function disturbances (transaminases increase) have been described.

ADVERSE REACTIONS

Many adverse reactions due to ASA ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature and from both clinical and post marketing experience.

Gastrointestinal (the frequency and severity of these adverse effects are dose-related): nausea, vomiting, diarrhea, gastrointestinal bleeding and/or ulceration, dyspepsia, heartburn, hematemesis, melena, abdominal pain, rarely gastrointestinal inflammation, and intestinal diaphragm disease with frequency not known (especially in long-term treatment).

Bleeding: Due to platelet inhibition, bleedings e.g. perioperative haemorrhage, hematomas, epistaxis, urogenital bleedings, and gingival bleedings may occur.

Serious bleedings, such as gastrointestinal tract hemorrhages, and cerebral hemorrhages are rare. Isolated cases of potentially life threatening bleedings have been reported, especially in patients with uncontrolled hypertension and/or concomitant antihemostatic agents.

Ear: dizziness, tinnitus, vertigo, hearing loss. Dizziness and tinnitus have been reported, which may be indicative of an overdose.

Hematologic: leukopenia, thrombocytopenia, purpura, anemia. Anemia with respective laboratory and clinical signs and symptoms, such as asthenia, pallor, and hypoperfusion is generally caused by bleeding (e.g. occult microbleeding, acute or chronic bleeding). Hemolysis

and hemolytic anemia in patients with severe forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency has been reported.

Dermatologic and hypersensitivity: urticaria, pruritus, skin eruptions, asthma, anaphylaxis, edema, nasal congestion and rhinitus. Severe allergic reactions, including anaphylactic shock are very rarely reported.

Miscellaneous: mental confusion, drowsiness, sweating, thirst. Transient hepatic impairment with increase in liver transaminases has very rarely been reported. Renal impairment and acute renal failure have been reported.

DRUG INTERACTIONS

Overview

ASA should be used with caution with other products that have anticoagulation or antiplatelet effects, as these effects may be potentiated. Drugs that bind to protein binding sites should also be used cautiously since ASA may displace drugs from their protein binding site.

Contraindicated Interactions

Methotrexate, used at doses of 15mg/week or more: Increased hematological toxicity of methotrexate (due to decreased renal clearance of methotrexate by anti-inflammatory agents in general and displacement of methotrexate from its plasma protein binding by salicylates). See "Contraindications".

Drug-Drug Interactions

Methotrexate, used at 15mg/week or less: Salicylates may retard the elimination of methotrexate by decreasing renal clearance of methotrexate, displacing methotrexate from protein binding sites, and thereby increasing its hematological toxicity.

Anti-coagulants, thrombolytics / other inhibitors of platelet aggregation / hemostasis, e.g. warfarin, heparin: Caution is necessary when salicylates and anticoagulants, thrombolytics / other inhibitors of platelet aggregation / hemostasis are prescribed concurrently, as salicylates can depress the concentration of prothrombin in the plasma, leading to an increased risk of bleeding.

Oral hypoglycemics, e.g. insulin, sulfonylureas: Large doses of salicylates have a hypoglycemic action and may enhance the effect of oral hypoglycemic agents. Diabetics receiving concurrent salicylate and hypoglycemic therapy should be monitored closely: reduction of the sulfonylurea hypoglycemic drug dosage may be necessary.

Diuretics: Diuretics in combination with acetylsalicylic acid at higher doses leads to decreased glomerular filtration via decreased prostaglandin synthesis. As a result, sodium excretion may be decreased by salicylate administration.

Uricosuric Agents: Salicylates in large doses are uricosuric agents; smaller amounts may depress uric acid clearance and thus decrease the uricosuric effects of other drugs.

Valproic Acid: Salicylates may alter valproic acid (VPA) metabolism and may displace VPA from protein binding sites, possibly intensifying the effects of VPA. Caution is recommended when VPA is administered concomitantly with salicylates.

Glucocorticoids (systemic), except hydrocortisone used as replacement therapy in Addison's disease: Decreased blood salicylate levels during corticosteroid treatment and risk of salicylate overdose after this treatment is stopped via increased elimination of salicylates by corticosteroids. Concurrent use may increase the incidence of gastrointestinal bleeding and ulceration.

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors *may* be diminished by the concomitant administration of ASA due to its indirect effect on the renin-angiotensin conversion pathway (i.e. inhibition of vasodilatory prostaglandins leading to decreased glomerular filtration). The potential interaction may be related to the dose of ASA (3g/day or more).

Selective Serotonin Re-uptake Inhibitors (SSRIs): Increased risk of upper gastrointestinal bleeding due to possibly synergistic effect.

Digoxin: Plasma concentrations of digoxin are increased due to a decrease in renal excretion.

NSAIDs:

ASA and other NSAIDs:

The use of other NSAIDs with salicylates at high doses (≥ 3g/day) may increase the risk of ulcers and gastrointestinal bleeding due to a synergistic effect.

Ibuprofen: Ibuprofen can interfere with the anti-platelet effect of low dose ASA acid (81 to 325 mg per day). Long-term daily use of ibuprofen may render ASA less effective when used for cardioprotection and stroke prevention. To minimize this interaction, regular users of ibuprofen and of low-dose, immediate-release ASA should take the ibuprofen at least one hour after and 11 hours before the daily ASA dose. The use of delayed-release (e.g. enteric-coated) ASA is not recommended when using ibuprofen regularly.

Naproxen: Naproxen may attenuate the irreversible platelet inhibition induced by acetylsalicylic acid. Clinical pharmacodynamic data suggest that concurrent (same day) naproxen sodium usage for more than one day consecutively inhibits the effect of low-dose acetylsalicylic acid on platelet activity and this inhibition may persist for up to several days after stopping naproxen sodium therapy. The clinical relevance of this interaction is not known. Treatment with naproxen, in patients with increased cardiovascular risk may limit the cardiovascular protection of acetylsalicylic acid (*see "Special warnings and precautions for use"*).

Healthcare professionals should advise consumers and patients regarding the appropriate concomitant use of NSAIDs (i.e. ibuprofen or naproxen) and ASA.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herb have not been established.

Drug-Laboratory Interactions
Salicylates can produce changes in thyroid function tests.

Drug-Lifestyle Interactions

Alcohol: Increased damage to gastrointestinal mucosa and prolonged bleeding time due to additive effects of acetylsalicylic acid and alcohol. Patients having 3 or more alcoholic drinks per day should consult their physician before use.

DOSAGE AND ADMINISTRATION

ASA tablets should preferably be taken after meals, with plenty of liquid.

Dosing Considerations
Please see below for specific dosing instructions for each indication.

Platelet aggregation inhibitor:

Suspected Acute Myocardial Infarction: An initial dose of at least 160 to 162.5 mg chewed to ensure rapid absorption as soon as a myocardial infarction is suspected. The same dose should be given as maintenance over the next 30 days. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI (see Prior Myocardial Infarction).

Prevention of a first non-fatal myocardial infarction: 80 to 325 mg once daily, according to the individual needs of the patient, as determined by the physician.

Prior Myocardial Infarction or Unstable Angina Pectoris: 80 to 325 mg daily according to the individual needs of the patient, as determined by the physician.

Transient Ischemic Attack and Secondary Prevention of Atherothrombotic Cerebral Infarction: 80 to 325 mg daily according to the individual needs of the patient, as determined by the physician.

Prophylaxis of Venous Thromboembolism after total hip replacement: 162 to 325 mg daily according to the individual needs of the patient, as determined by the physician.

OVERDOSAGE

Mild Overdose or Early Poisoning - burning in the mouth, lethargy, nausea, vomiting, tinnitus, sweating, thirst, tachycardia or dizziness.

Moderate Overdose - all of the symptoms from mild overdose plus tachypnea, hyperpyrexia, sweating, dehydration, loss of coordination, restlessness, mental confusion.

Severe Overdose - all of the symptoms from moderate overdose plus hypotension, hallucinations, stupor, hypoglycemia, convulsions, cerebral edema, oliguria, renal failure, cardiovascular failure, coma, hemorrhage, metabolic acidosis, respiratory alkalosis and/or failure.

Emergency Management:

1. Immediate transfer to hospital and maintain cardiovascular and respiratory support.
2. Gastric lavage, administration of activated charcoal,
3. Check of acid-base balance and correct if necessary.
4. Alkaline diuresis so as to obtain urine pH between 7.5 and 8 should be considered when plasma salicylate concentration is greater than 500mg/L (3.6 mmol/L) in adults or 300mg/L (2.2 mmol/L) in children
5. Hemodialysis should be considered in severe poisoning 800mg/L (5.8 mmol/L) in adults and 700mg/L (5.0 mmol/L) in children, as renal elimination of salicylates may be slow due to the presence of acidic urine and renal failure. Hemodialysis should also be considered if the patient is experiencing severe systemic metabolic acidosis (arterial pH < 7.2), acute renal failure, pulmonary edema or CNS symptoms such as: drowsiness, agitation, coma or convulsions.
6. Fluid losses should be replaced with hypotonic solution (e.g. half saline) and supplemented with glucose 50 to 100g/L.
7. Symptomatic treatment.

Fatal Dose: varies from 10 to 30g of ASA. However, (in one case) 130g of ASA was ingested without fatal outcome.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ASA interferes with the production of prostaglandins in various organs and tissues through acetylation of the enzyme cyclo-oxygenase. Prostaglandins are themselves powerful irritants and produce headaches and pain on injection in man. Prostaglandins also appear to sensitize pain receptors to other noxious substances such as histamine and bradykinin. By preventing the synthesis and release of prostaglandins in inflammation, ASA may avert the sensitization of pain receptors.

The antipyretic activity of ASA is due to its ability to interfere with the production of prostaglandin E_1 in the brain. Prostaglandin E_1 is one of the most powerful pyretic agents known. 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.

In vitro studies have shown that ASA enhances the activity of the Nitric oxide (NO)-cGMP system and heme oxygenase-1 (HO-1) by acting on endothelial NO synthase site.

Pharmacokinetics

Absorption:

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 1.0mg % 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 7mg %. 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:

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.

Metabolism:

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:

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.

With the administration of 325mg, elimination of ASA is linear following a first order kinetics. At high concentrations, elimination half life increases.

Special Populations and Conditions:

Absorption and clearance of salicylates are not affected by gender or age.

STORAGE AND STABILITY

Store at room temperature 15°C to 30°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each blue, round enteric coated tablet, engraved 'APO' on one side '81' on other side, contains 81 mg acetylsalicylic acid.

Available in bottles of 8, 24, 30, 90, 100, 120, 125, 150, 180, 240, 250, 500 and 1000 tablets.

Each APO-ASA LD round blue tablet contains 81 mg of acetylsalicylic acid and the non-medicinal ingredients, corn starch, FD&C blue #1, hydroxypropyl methylcellulose, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, talc, titanium dioxide and triethyl citrate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

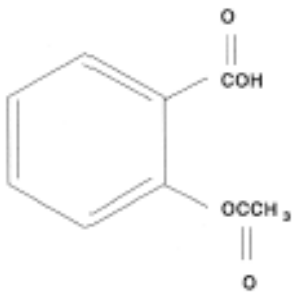
Proper Name: Acetylsalicylic acid

Chemical Name: 2-(Acetyloxy) benzoic acid; salicylic acid acetate

Molecular formula: $C_9H_8O_4$

Molecular mass: 180.16 g/mol

Structural Formula:



Physicochemical properties:

Description: White granular powder.

Solubility: Solubility in common solvents at 25°C:

Solvent	**Solubility** (parts of solvent required for 1 part of solute)	**Descriptive Term** (as defined in the USP)
Alcohol	From 1 to 10	Freely soluble
Chloroform / Ether	From 10 to 30	Soluble
Absolute Ether	From 30 to 100	Sparingly soluble
Water	From 100 to 1000	Slightly soluble

Solubility in 0.1N HCL

°C	mg/mL
30°C	4.25
37°C	5.65
50°C	8.8

pK value (25°C): 3.49

Melting point: 135°c (rapid heating)

CLINICAL TRIALS

COMPARATIVE BIOAVAILABILITY

A comparative bioavailability study was performed on healthy male human volunteers under fasting conditions. The rate and extent of absorption of salicylic acid was measured and compared following a single oral dose of APO-ASA LD (acetylsalicylic acid) and Aspirin® 81mg Delayed Release tablets. The results from measured data are summarized in the following table:

Salicylic Acid

(n=23)

3 x 81 mg ASA (acetylsalicylic acid) Enteric Coated Tablets - Fasted State

From measured data

uncorrected for potency

Geometric Mean

Arithmetic Mean (CV %)

Parameter	APO-ASA LD Test	Aspirin®€ Reference	% Ratio of Geometric Means#	90% Confidence Interval#
AUC_T (ng•h/mL)	52449 53188 (17)	54697 55738 (20)	95.9	93.3 – 98.5
AUC_I (ng•h/mL)	53836 54691 (18)	55722 56873 (21)	96.6	94.0 – 99.3
C_{max} (ng/mL)	10220 10317 (14)	11330 11490 (17)	89.9	84.9 – 95.2
T_{max}§ (h)	5.39 (16)	4.59 (19)		
$T_{1/2}$§ (h)	2.10 (15)	2.03 (15)		

€ Aspirin® Coated Daily Low Dose (acetylsalicylic acid) 81 mg enteric coated tablets, Bayer Canada, purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only.
# based on least squares estimates.

Study demographics and trial design

Anti-Platelet Aggregation Studies

Study #/ cross-reference	Trial Design	Dosage, route of administration and duration	Study Subjects (n = number)	Mean age (Range)	Gender
Indication: Reducing the risk of vascular mortality in patients with a suspected acute myocardial infarction.					
ISIS – 2 Ref 73	Multicentre international 2x2 factorial, randomized, placebo controlled study.	160-162.5 mg oral for 30 days after suspected acute MI. (Median follow-up to 15 months).	ASA 8587, Streptokinase 8592, ASA + Strep 4292, Placebo 4300	Not available	Not available
Indication: Reducing the risk of a first non-fatal myocardial infarction in individuals deemed to be at sufficient risk of such an event by their physician					
TPT Ref 91	Randomized, factorial, placebo-controlled, parallel-group study	warfarin (mean) 4.1mg, ASA 75mg	warfarin + ASA 1,277 warfarin + ASA placebo 1,268 ASA + warfarin placebo 1,268 ASA placebo + warfarin placebo 1,272	45-69 years	Male
HOT Ref 59	Prospective, randomized, open with blinded endpoint evaluation (PROBE). ASA component was double blinded	ASA 75mg or placebo; felodipine 5mg, ACE-inhibitors, β-blockers, diuretics mean - 3.8 years	19,567 subjects of which 18,790 were randomized to ASA or Placebo (ASA = 9,399; Placebo = 9,391)	61.5 years - mean (50-80 years)	Male 53% Female 47%
PHS Ref 130	Double blind placebo controlled, 2x2 factorial randomized parallel group	ASA 325mg every other day for 60.2 months	22,071 ASA = 11,037 Placebo = 11,034	40 to 84 years	Male
Indication: Reducing the risk of morbidity and death in patients with unstable angina and in those with previous myocardial infarction					
RISC Ref 114	Prospective randomized, double blind, placebo controlled, multicentre study	ASA 75mg daily for 3 months after initial heparin by IV for 5 days	-Heparin 198 -ASA 189 -Heparin + ASA 210 -Placebo 199	58 years	Male
RISC Trial, 12 month follow-up	Prospective randomized, double blind, placebo controlled,	ASA 75mg daily for 3 months after initial IV heparin for 5 days	-Heparin 198 -ASA 189 -Heparin + ASA 210	58 years	Male

Study #/ cross-reference	Trial Design	Dosage, route of administration and duration	Study Subjects (n = number)	Mean age (Range)	Gender
Ref 137	multicentre study		-Placebo 199		
Verheugt et al. Ref 136	Prospective, randomized, placebo-controlled, comparative multicentre study	ASA 100mg for approx. 3 months	ASA 50 Placebo 50	ASA 61 years Placebo 64 years	ASA 72% male Placebo 76% male
SAPAT Ref 77	Prospective, randomized, double blind placebo controlled, multicentred study	ASA 75mg daily for up to 6 years (median 50 months)	ASA 1009 Placebo 1026	52 years	ASA male 51% Placebo males 53%
Indication: Reducing the risk of transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction					
SALT Ref 120	Prospective, randomized, double blind, placebo controlled, multicentre study	ASA 75mg daily for minimum of 12 months and maximum of 63 months (mean 30.6 months)	ASA 676 Placebo 684	50-79 years ASA mean: 67 years PLA mean: 66.8 years	ASA 65.4% male Placebo 66.2% male
Lindblad et al. Ref 85	Prospective, randomized, double blind placebo controlled study	ASA 75mg daily for 6 months	ASA 117 Placebo 115	66 years (40-81 years)	75% male

Study results

Platelet Aggregation Studies Results

Study #	Primary Endpoints	Associated value and statistical significance for ASA compared to Placebo and Comparator	
Indication: Reducing the risk of vascular mortality in patients with a suspected acute myocardial infarction.			
		Value	ASA vs. Placebo
ISIS – 2 Ref 72	Vascular death after 5 week period	ASA 9.4%, Placebo 11.8% Odds reduction 23%	2p < 0.00001 ASA was statistically significantly better than placebo
Indication: Reducing the risk of a first non-fatal myocardial infarction in individuals deemed to be at sufficient risk of such an event by their physician			

Study #	Primary Endpoints	Associated value and statistical significance for ASA compared to Placebo and Comparator		
TPT Ref 91	All ischemic heart disease defined as the sum of fatal and non-fatal events (i.e. coronary death and fatal and non-fatal myocardial infarction).	ASA 10.2%, Placebo 13.3% 20% reduction in IHD	p = 0.04 ASA was statistically significantly better than placebo	
HOT Ref 59	Major cardiovascular events were defined as all (fatal and non-fatal) myocardial infarctions, all (fatal and non-fatal) strokes, and all other cardiovascular deaths.	Reduction in all cardiovascular events by 15 % and all myocardial infarction by 36%	p=0.03 p = 0.002 ASA was statistically significantly better than placebo	
PHS Ref 130	fatal and non-fatal myocardial infarction	325 mg ASA every other day: 44% reduction in risk of MI in ASA vs. Placebo group Relative Risk 0.56, 95% CI 0.45-0.70	p<0.00001 P<0.0001 ASA was statistically significantly better than placebo	
Indication: Reducing the risk of morbidity and death in patients with unstable angina and in those with previous myocardial infarction				
		Value	ASA vs. Placebo	ASA vs. Comparator
RISC Ref 114	Death or non-fatal MI	5 days: Risk Ratio 0.43 (CI 0.21-0.91) 30 days: Risk Ratio 0.31 (CI 0.18-0.53) 90 days: Risk Ratio 0.36 (0.21-0.57)	p=0.03 p<0.0001 p<0.0001 ASA was statistically significantly better than placebo	Heparin was not statistically significantly better than placebo and there was no comparison to ASA
RISC Trial, 12 month follow-up Ref 137	MI and death	6 months: ASA-35 events, heparin 76 events. Risk Ratio 0.46 (CI 0.31-0.67) 12 months, ASA 44 events, heparin 85 events. Risk Ratio 0.52 (CI 0.37-0.72)	p<0.0001 p=0.0001 ASA was statistically significantly better than placebo	Not Performed
Verheugt et al. Ref 85	Reinfarction rate	ASA 2 patients (4%), Placebo 9 patients (18%)	p<0.03 ASA was statistically significantly better than placebo	Not Performed

Study #	Primary Endpoints	Associated value and statistical significance for ASA compared to Placebo and Comparator		
SAPAT Ref 77	non-fatal or fatal MI or sudden death	ASA 8%, Placebo 12%	p=0.003 ASA was statistically significantly better than placebo	Not Performed
Indication: Reducing the risk of transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction				
		Value	ASA vs. Placebo	
SALT Ref 120	Risk of stroke or death	18 % reduction in risk: Relative Risk 0.82 (CI 0.67-0.99)	p=0.02 ASA was statistically significantly better than placebo	
Lindblad et al. Ref 85	Stroke (without complete recovery) at 6 months	ASA 2 cases, Placebo 11 cases	p=0.01 ASA was statistically significantly better than placebo	

DETAILED PHARMACOLOGY

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. ASA 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, ASA 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 ASA thus persists 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 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.

The use of ASA in patients with a suspected acute myocardial infarction was investigated in a large multi-centre trial involving over 17,000 patients. Treatment with ASA resulted in a 23% reduction in the risk of vascular mortality versus placebo at 5 weeks. This use translates to a reduction of 24 deaths and 14 non-vascular events per 1000 patients treated.

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% versus 21%, versus 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 to 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 to 1200 mg/day), indicated that the incidence of gastrointestinal adverse effects were significantly less common with the lower doses.

In a study in patients undergoing coronary artery bypass surgery (CABG), patients given ASA at a dosage of 80 mg to 650 mg within 48 hours of revascularization had a risk of dying reduced to 1.3% as compared to 4.0% for those who did not receive treatment ($P<0.001$). There was a reduction in the incidence of myocardial infarction of 2.8% vs. 5.4%, $p < 0.001$. In total, the reduction in fatal and non-fatal outcomes was lower in those who received ASA, 10.6% vs. 18.6% in those who did not ($p<0.001$). The investigators Perioperative Ischemia Research Group (PIRG) concluded that early use of ASA after coronary by-pass surgery is safe and is associated with a reduce risk of death and ischemic complications involving the heart, brain, kidneys and gastrointestinal tract.

There was no ASA dose effect observed for either fatal or non-fatal outcomes with total doses lower than 325mg daily.

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) 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 ASA against the clearly established reduction in the incidence of a first myocardial infarction".

Effect of Ibuprofen on Platelet Aggregation, Bleeding and Clotting Times in Normal Volunteers:

Experimental data suggest that ibuprofen may inhibit the effect of low dose ASA (81 to 325 mg per day) on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release ASA dosing (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use. In a more recent double blind, randomized, placebo-controlled trial with healthy subjects by Cryer et. al, 2005, it has been shown that the drug-drug interaction is absent when immediate release ASA (81 mg) was taken 1 hour before taking ibuprofen (400 mg, TID) and also when ibuprofen was given 11 hours before the intake of low dose ASA. Thus, in order to adequately minimize potential interaction, the recommended dosing schedule for immediate release low dose ASA is to wait at least 11 hours after or 1 hour before taking up to a 400mg dose of ibuprofen.

MICROBIOLOGY

Not applicable

TOXICOLOGY

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

The acute toxicity 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 man, 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 man, 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.

Chronic toxicity 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 0.24 g/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, piloerection, 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 man.

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200. ASPIRIN® Regular Strength, (acetylsalicylic acid tablets USP, 325mg), ASPIRIN® Extra Strength (acetylsalicylic acid tablets USP, 500mg), ASPIRIN® 81mg (acetylsalicylic acid delayed release tablets USP, 81mg) and ASPIRIN® 81mg Quick Chews® (acetylsalicylic acid tablets USP, 81mg), Submission Control Number: 248124, Product Monograph, BAYER INC; Date of Revision: May 19, 2021.

PART III: CONSUMER INFORMATION

APO-ASA LD
Acetylsalicylic Acid Delayed-Release Tablets, USP
81 mg

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

ABOUT THIS MEDICATION

What the medication is used for:
- APO-ASA LD is for doctor supervised long-term preventive therapy.
- APO-ASA LD may help save your life if you think you are having a heart attack.

What it does:
APO-ASA LD 81 mg is for doctor supervised long-term preventive therapy.

USE DURING A HEART ATTACK
If you think you are having a heart attack, call 911 immediately then, chew and swallow two APO-ASA LD. It is important to chew the product, to ensure this medicine works quickly. Then get to a hospital immediately for medical attention. Inform the emergency services / hospital that you have taken APO-ASA LD. Taking APO-ASA LD, at the first signs and symptoms can reduce your risk of dying from the heart attack.

The signs and symptoms of a heart attack include:
- uncomfortable pressure, fullness, squeezing or pain in the centre of the chest that lasts more than a few minutes, or goes away quickly and comes back,
- pain that spreads to the shoulders, neck or arms,
- chest discomfort with lightheadedness, fainting, sweating, nausea or shortness of breath.

Chest pain is the most common symptom in both sexes, but women may also experience other symptoms such as unusual fatigue that gets worse with activity, difficulty of breathing, heartburn/nausea and /or vomiting unrelieved by antacids, tightening and pain in the chest that may extend into the neck, jaws and shoulders, general feeling of weakness, paleness, sweating.

At the hospital, the doctor will then recommend appropriate therapy.

When it should not be used:

DO NOT TAKE APO-ASA LD if you:
- are allergic to ASA, salicylates, non-steroidal anti-inflammatory drugs (NSAIDs)/pain relievers/fever reducers, or other ingredients in the product
- have an ulcer, history of ulcers or are prone to bleeding
- have active or severe liver or kidney disease or congestive heart failure
- have a history of asthma caused by salicylates or other NSAIDs.
- are using methotrexate at doses of 15 mg/week or more
- are in the last trimester of pregnancy because it may cause problems in the unborn child or complications during delivery

What the medicinal ingredient is:
acetylsalicylic acid (ASA).

What the important nonmedicinal ingredients are:
corn starch, FD&C blue # 1, hydroxypropyl methylcellulose, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, talc, titanium dioxide and triethyl citrate.

What dosage forms it comes in:
APO-ASA LD, 81 mg is only available as tablets for oral use.

WARNINGS AND PRECAUTIONS

Your doctor will have asked you many questions about your health, lifestyle, and medications before recommending APO-ASA LD. That is why it is very important that you tell your doctor all such information. If you have forgotten to tell your doctor about any of the following, call your doctor or pharmacist before you take this medicine (or any medicine):

- asthma, high blood pressure, heart disease, gout or other serious conditions;
- age 60 years or older;
- stomach problems such as heartburn, **STOMACH BLEEDING WARNING**: contains NSAID which **may cause severe stomach bleeding**;
- impaired liver/kidney disease or impaired cardiovascular circulation (renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or major hemorrhagic events;
- have history of blood clotting defects;
- severe anemia;

- severe glucose-6-phosphate dehydrogenase (G6PD) deficiency;
- are trying to conceive, pregnant or breast-feeding; or
- will be having surgery in five to seven days

CAUTION: Contains enough drug to seriously harm a child; **KEEP OUT OF THEIR REACH. DO NOT GIVE** to children/teenagers less than 18 years of age who have chicken pox or cold/flu symptoms before a doctor is consulted about Reye's Syndrome, a rare serious illness reported to be associated with ASA.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you are taking any prescription or non- prescription drugs including blood thinners, acetaminophen, anticonvulsants, anti-diabetic/arthritis/gout medicines, digoxin, glucocorticoids, methotrexate, selective-serotonin re-uptake inhibitors (a type of antidepressant), diuretics, ACE inhibitors (medication for high blood pressure), or if you are having 3 or more alcoholic drinks per day.

Do not use NSAIDs (i.e. ibuprofen or naproxen) if you are taking APO-ASA LD 81 mg for preventive therapy without talking to a doctor or pharmacist, as NSAIDs may interfere with the preventive benefits of APO-ASA LD 81 mg .

PROPER USE OF THIS MEDICATION

Usual dose:
DIRECTIONS (Adults ≥18 years):
For doctor supervised long-term preventive therapy:
1 to 4 tablets daily, depending on your doctor's instructions. You should take this medicine at the same time every day. This will help you to remember to take your medication. For maximum effectiveness, it is very important to take APO-ASA LD 81 mg every day as directed by your doctor. Do not take more tablets than your doctor recommends. Your doctor may tell you to take APO-ASA LD 81 mg with other medications; he or she may also tell you to eat special foods, exercise or take other steps to safeguard your health. APO-ASA LD 81 mg tablets have a special enteric coating, which allows them to pass undissolved through the stomach and into the intestine. By dissolving in the intestine rather than the stomach, the risk of stomach upset is reduced. Therefore, to maintain this protection, the tablets should not be crushed or broken.

During a heart attack: Call 911, then, **chew** 2 – APO-ASA LD tablets.

Can I Continue to Take APO-ASA LD for Relief of Headache, Fever or Arthritis Pain?

APO-ASA LD is specially designed for doctor supervised long-term preventive therapy. It is a smaller dose than you would need to take for a headache or other types of pain and is unlike other pain reliever products such as acetaminophen or NSAIDs e.g., ibuprofen, naproxen. Ask your doctor or pharmacist about other APO-ASA LD 81 mg products available (or other pain relievers such as acetaminophen, ibuprofen, naproxen or salicylates) and the correct dosage for the relief of your headache, fever or arthritic pain.

Always consult with your doctor or pharmacist before taking other medications.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-ASA LD, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take your medication, take it when you remember. But do not take *extra* medication to compensate for a missed dosage unless instructed by your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, APO-ASA LD may occasionally produce unwanted side effects. You should call your doctor if you experience: nausea, vomiting; stomach irritation, or pain; if you notice that you are 'bruising' more easily than you were before starting a daily dose of APO-ASA LD. Regular daily use of alcohol while on APO-ASA LD daily therapy may increase your risk of developing gastrointestinal bleeding.
This is not a complete list of side effects. For any unexpected effects while taking APO-ASA LD, contact your doctor or pharmacist.

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

Stop use and call your doctor if you experience an allergic reaction (skin rash, hives, itching, swelling of the eyes, face, lips, tongue, or throat, wheezing or breathing difficulties); stomach bleeding (feel faint, bloody vomit, vomit that looks like coffee grounds, bright red blood in stools, black or tarry stools, stomach pain that does not get better); loss of hearing, ringing or buzzing in ears or bleeding.

HOW TO STORE IT

Keep out of reach of children.

Store at room temperature 15°C to 30°C.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about APO-ASA LD:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html). Find the Consumer Information on the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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