years of age: oral dosage is 6.25 milligrams every 4 hours, not to exceed 37.5 milligrams in 24 hours.

§ 343.22 Permitted combinations of active ingredients for cardiovascular-rheumatologic use.

Combinations containing aspirin must meet the standards of an acceptable dissolution test, as set forth in §343.90. The following combinations are permitted: Aspirin identified in §§343.12 and 343.13 may be combined with any antacid ingredient identified in §331.11 of this chapter or any combination of antacids permitted in accordance with
COMPREHENSIVE PRESCRIBING INFORMATION

DESCRIPTION

(Insert the proprietary name and the established name (if any) of the drug, type of dosage form (followed by the phrase "for oral administration"), the established name(s) and quantity of the active ingredient(s) per dosage unit, the total sodium content in milligrams per dosage unit if the sodium content of a single recommended dose is 5 milligrams or more, the established name(s) (in alphabetical order) of any inactive ingredient(s) which may cause an allergic hypersensitivity reaction, the pharmacological or therapeutic class of the drug, and the chemical name(s) and structural formula(s) of the drug. Aspirin is an odorless white, needle-like crystalline or powdery substance. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary-odor. It is highly lipid soluble and slightly soluble in water.

PHARMACOKINETICS

MECHANISM OF ACTION: Aspirin is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than other salicylic acid derivatives. The differences in activity between aspirin and salicylic acid are thought to be due to the acetyl group on the aspirin molecule. This acetyl group is responsible for the inactivation of cyclooxygenase via acetylation.

PHARMACOKINETICS

ABSORPTION: In general, immediate release aspirin is well and completely absorbed from the gastrointestinal (GI) tract. Following absorption, aspirin is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1-2 hours of dosing (see Pharmocokinetics—Metabolism). The rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH (the presence or absence of GI antacids or buffering agents), and other physiologic factors. Enteric coated aspirin products are erratically absorbed from the GI tract.

DISTRIBUTION: Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk, and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylate is concentration-dependent, i.e., nonlinear. At low concentrations (<100 micrograms/milliliter (μg/mL)), approximately 90 percent of plasma salicylate is bound to albumin while at higher concentrations (>400 μg/mL), only about 70 percent is bound. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approximating 200 μg/mL. Severe toxic effects are associated with levels >400 μg/mL. (See Adverse Reactions and Overdose.)

METABOLISM: Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin are essentially undetectable 1-2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acetyl glucuronide, and a number of minor metabolites. Salicylic acid has a plasma half-life of approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicylic acid and phenolic glucuronide. Following toxic doses (10-20 grams (g)), the plasma half-life may be increased to over 20 hours.

ELIMINATION: The elimination of salicylic acid follows zero order pharmacokinetics; (i.e., the rate of drug elimination is constant in relation to plasma concentration). Renal excretion of unchanged drug depends upon
INDICATIONS AND USAGE

Vascular Indications (Ischemic Stroke, TIA, Acute MI, Prevention of Recurrent MI, Unstable Angina Pectoris, and Chronic Stable Angina Pectoris): Aspirin is indicated to: (1) Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, (2) reduce the risk of vascular mortality in patients with a suspected acute MI, (3) reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, and (4) reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.

Revascularization Procedures (Coronary Artery Bypass Graft (CABG), Percutaneous Transluminal Coronary Angioplasty (PTCA), Transluminal Coronary Angioplasty (PTCA), and Chronic Stable Angina Pectoris: Aspirin is indicated in patients with unstable angina pectoris who undergo revascularization procedures if there is a preexisting condition for which aspirin is already indicated.
CONTRAINDICATIONS

Allergy: Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma).

Reye’s Syndrome: Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye’s syndrome with concomitant use of aspirin in certain viral illnesses.

WARNINGS

Alcohol Warning: Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

Coagulation Abnormalities: Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders.

GI Side Effects: GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

Pep tic Ulcer Disease: Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

PRECAUTIONS

General

Renal Failure: Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute).

Hepatic Insufficiency: Avoid aspirin in patients with severe hepatic insufficiency.

Sodium Restricted Diets: Patients with sodium-retaining states, such as congestive heart failure or renal failure, should avoid sodium-containing buffered aspirin preparations because of their high sodium content.

Laboratory Tests

Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

Drug Interactions

Angiotensin Converting Enzyme (ACE) Inhibitors: The hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.

Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant Therapy (Heparin and Warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and the effect on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.

Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired.

Nonsteroidal Anti-inflammatory Drugs (NSAID’s): The concurrent use of aspirin with other NSAID’s should be avoided because this may increase bleeding or lead to decreased renal function.

Oral Hypoglycemics: Moderate doses of aspirin may increase the effectiveness of oral
hypoglycemic drugs, leading to hypoglycemia.

**Uricosuric Agents (Probenecid and Sulfinpyrazone):** Salicylates antagonize the uricosuric action of uricosuric agents.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Administration of aspirin for 68 weeks at 6.5 percent in the feed of rats was not carcinogenic. In the Ames Salmonella assay, aspirin was not mutagenic; however, aspirin did induce chromosome aberrations in cultured human fibroblasts. Aspirin inhibits ovulation in rats. (See Pregnancy.)

**Pregnancy:** Pregnant women should only take aspirin if clearly needed. Because of the known effects of NSAID’s on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and perinatal mortality.

**Labor and Delivery:** Aspirin should be avoided 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

**Nursing Mothers:** Nursing mothers should avoid using aspirin because salicylate is excreted in breast milk. Use of high doses may lead to rashes, platelet abnormalities, and bleeding in nursing infants.

**Pediatric Use:** Pediatric dosing recommendations for juvenile rheumatoid arthritis are based on well-controlled clinical studies. An initial dose of 90–130 mg/kg/day in divided doses, with an increase as needed for anti-inflammatory efficacy (target plasma salicylate levels of 150–300 μg/mL) are effective. At high doses (i.e., plasma levels of greater than 300 μg/mL), the incidence of toxicity increases.

### ADVERSE REACTIONS

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature. (See Warnings.)

**Body as a Whole:** Fever, hypothermia, thirst.

**Cardiovascular:** Dysrhythmias, hypotension, tachycardia.

**Central Nervous System:** Agitation, cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures.

**Fluid and Electrolyte:** Dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis.

**Gastrointestinal:** Dysepsia, GI bleeding, ulceration and perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye’s Syndrome, pancreatitis.

**Hematologic:** Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia.

**Hypersensitivity:** Acute anaphylaxis, angioedema, asthma, bronchoospasm, laryngeal edema, urticaria.

**Musculoskeletal:** Rhabdomyolysis.

**Metabolism:** Hypoglycemia (in children), hyperglycemia.

**Reproductive:** Prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding.

**Respiratory:** Hyperpnea, pulmonary edema, tachypnea.

**Special Senses:** Hearing loss, tinnitus. Patients with high frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.

**Urogenital:** Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure.

### DRUG ABUSE AND DEPENDENCE

Aspirin is nonnarcotic. There is no known potential for addiction associated with the use of aspirin.

### OVERDOSAGE

Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approaching 200 μg/mL. Plasma concentrations of aspirin above 300 μg/mL are clearly toxic. Severe toxic effects are associated with levels above 400 μg/mL. (See CLINICAL PHARMACOLOGY.) A single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g. For real or suspected overdose, a Poison Control Center should be contacted immediately. Careful medical management is essential.

**Signs and Symptoms:** In acute overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis.

**Treatment:** Treatment consists primarily of supporting vital functions, increasing salicylate elimination, and correcting the acid-base disturbance. Gastric emptying and/or lavage is recommended as soon as possible after ingestion, even if the patient has vomited spontaneously. After lavage and/or emesis, administration of activated charcoal, as a slurry, is beneficial, if less than 3 hours have passed since ingestion. Charcoal adsorption should not be employed prior to emesis and lavage.

**Severity of aspirin intoxication is determined by measuring the blood salicylate level. Acid-base status should be closely followed with serial blood gas and serum pH.
measurements. Fluid and electrolyte balance should also be maintained.

In severe cases, hyperthermia and hypovolemia are the major immediate threats to life. Children should be sponged with tepid water. Replacement fluid should be administered intravenously and augmented with correction of acidosis. Plasma electrolytes and pH should be monitored to promote alkaline diuresis of salicylate if renal function is normal. Infusion of glucose may be required to control hypoglycemia.

Hemodialysis and peritoneal dialysis can be performed to reduce the body drug content. In patients with renal insufficiency or in cases of life-threatening intoxication, dialysis is usually required. Exchange transfusion may be indicated in infants and young children.

DOSAGE AND ADMINISTRATION

Each dose of aspirin should be taken with a full glass of water unless patient is fluid restricted. Anti-inflammatory and analgesic dosages should be individualized. When aspirin is used in high doses, the development of tinnitus may be used as a clinical sign of elevated plasma salicylate levels except in patients with high frequency hearing loss.

Ischemic Stroke and TIA: 50–325 mg once a day. Continue therapy indefinitely.

Suspected Acute MI: The initial dose of 160–162.5 mg is administered as soon as an MI is suspected. The maintenance dose of 160–162.5 mg a day is continued for 30 days post-infarction. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI.

Prevention of Recurrent MI: 75–325 mg once a day. Continue therapy indefinitely.

Unstable Angina Pectoris: 75–325 mg once a day. Continue therapy indefinitely.

Chronic Stable Angina Pectoris: 75–325 mg once a day. Continue therapy for 1 year post-procedure.

PTCA: The initial dose of 325 mg should be given 2 hours pre-surgery. Maintenance dose is 160–325 mg daily. Continue therapy indefinitely.

CABG: 325 mg daily starting 6 hours post-procedure. Continue therapy indefinitely.

Spondyloarthropathies: Up to 4 g per day in divided doses.

Osteoarthritis: Up to 3 g per day in divided doses.

Arthritis and Pleurisy of SLE: The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 180–300 μg/mL. At high doses (i.e., plasma levels of greater than 200 μg/mL), the incidence of toxicity increases.

HOW SUPPLIED

(Insert specific information regarding, strength of dosage form, units in which the dosage form is generally available, and information to facilitate identification of the dosage form as required under § 201.57(k)(1), (k)(2), and (k)(3).

Store in a tight container at 25 °C (77 °F); excursions permitted to 15–30 °C (59–86 °F).


(2) In addition to, and immediately preceding, the labeling required under paragraph (a)(1) of this section, the professional labeling may contain the following highlights of prescribing information in the exact language and exact format provided, but only when accompanied by the comprehensive prescribing information required in paragraph (a)(1) of this section.
Food and Drug Administration, HHS

§ 343.80

(HIGHLIGHTS OF PRESCRIBING INFORMATION
ACETYLSALICYLIC ACID)

PROFESSIONAL INDICATIONS AND USAGE

Vascular Indications:
- Ischemic Strokes and Transient Ischemic Attacks (TIA)
- Suspected Acute Myocardial Infarction (MI)
- Prevention of Recurrent MI
- Unstable Angina Pectoris
- Chronic Stable Angina Pectoris

Revascularization Procedures in Select Patients:
- Coronary Artery Bypass Grafting (CABG)
- Percutaneous Transluminal Coronary Angioplasty (PTCA)
- Coronary Endarterectomy

Rheumatologic Disease Indications:
- Rheumatoid Arthritis
- Juvenile Rheumatoid Arthritis
- Spondylarthropathies
- Osteoarthritis
- Arthritis and Polyarthritis of Systemic Lupus Erythematosus (SLE)

Warfarin Use

Patients with a pre-existing condition for which aspirin is already indicated
See “Pharmacokinetic Parameters” under the “Indications and Usage” and “Clinical Studies” sections in the Comprehensive Prescribing Information.

General:
Each dose should be taken with a full glass of water unless otherwise indicated. Dose may need to be individualized depending on indication.

Indications | Recommended Daily Dose | Duration of Therapy |
--- | --- | ---
Vascular Indications: | | |
Ischemic Strokes and TIA | 30-325 milligrams (mg) daily | indefinitely |
Suspected Acute MI | 150-182.5 mg taken as soon as infection is suspected, then once daily | For 30 days post infection (after 30 days consider further treatment based on indication for previous MI) |
Prevention of Recurrent MI | 75-325 mg daily | indefinitely |
Unstable Angina Pectoris | 75-325 mg daily | indefinitely |
Chronic Stable Angina Pectoris | 75-325 mg daily | indefinitely |

Revascularization Procedures in Select Patients:
- CABG 305 mg daily starting 6 hrs. postprocedure 1 year
- PTCA 325 mg 2 hours preprocedure Maintenance therapy: 150-325 mg daily
- Coronary Endarterectomy 80 mg daily to 650 mg before a day started preprocedure indefinitely

Rheumatologic Disease Indications:
- Rheumatoid Arthritis Initial dose 3 g daily Target plasma salicylate levels 150-300 microgram/ml (μg/mL) As indicated
- Juvenile Rheumatoid Arthritis Initial dose 50-130 mg/kg/day Target plasma salicylate levels 150-300 μg/mL As indicated
- Spondylarthropathies Up to 4 grams (g) daily As indicated
- Osteoarthritis Up to 3 g daily As indicated
- Arthritis and Polyarthritis of SLE Initial dose 3 g daily Target plasma salicylate levels 150-300 μg/mL As indicated

CONTRAINDICATIONS
Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drugs and in patients with the syndromes of asthma, rhinitis, and nasal polyps. Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye’s syndrome with concurrent use of aspirin in certain viral illnesses.

PRECAUTIONS
General
- Nasal Failure
- Hepatic Insufficiency
- Sodium Restriction
- Laboratory Tests
- Drug Interactions
- Indication: Angiotensin-Converting Enzyme (ACE) inhibitors
- Acetylsalicylic Anticoagulant Therapy
- Anticoagulants
- Beta Blockers
- Decrest
- Methotrexate
- Nonsteroidal Anti-inflammatory Drugs (NSAID) 
- Oral Hypoglycemics
- Uncommon Agents
- Cocagon, Mallorin, Impairment of Fertility
- Pregnancy, Labor and Delivery, Nursing Mothers
- Pediatric Use

WARNINGS
- Alcohol Warning
- Coagulation Reactions
- Gastrointestinal Side Effects
- Peptic Ulcer Disease
- ADVERSE REACTIONS (Most common)
- Gastrointestinal Abdominal Pain, Ulceration, Bleeding
- Inhibition of Platelet Aggregation (Bleeding)
- Thrombosis
- Dizziness
- Hearing Loss
- To report SUSPECTED adverse drug reactions with WARFARIN at phone number 1-800-332-1572 at 1-800-332-1572.
- ADVERSE REACTIONS
- Acetylsalicylic Anticoagulant Therapy
- Anticoagulants
- Beta Blockers
- Decrest
- Methotrexate
- Nonsteroidal Anti-inflammatory Drugs (NSAID) 
- Oral Hypoglycemics
- Uncommon Agents
- Cocagon, Mallorin, Impairment of Fertility
- Pregnancy, Labor and Delivery, Nursing Mothers
- Pediatric Use

(b) [Reserved]

§ 343.90 Dissolution and drug release testing.

(a) [Reserved]

(b) Aspirin capsules. Aspirin capsules must meet the dissolution standard for aspirin capsules as contained in the United States Pharmacopeia (USP) 23 at page 132.

(c) Aspirin delayed-release capsules and aspirin delayed-release tablets. Aspirin delayed-release capsules and aspirin delayed-release tablets must meet the drug release standard for aspirin delayed-release capsules and aspirin delayed-release tablets as contained in USP 23 at pages 133 and 136 respectively.

(d) Aspirin tablets. Aspirin tablets must meet the dissolution standard for aspirin tablets as contained in USP 23 at page 134.

(e) Aspirin, alumina, and magnesia tablets. Aspirin in combination with alumina and magnesia in a tablet dosage form must meet the dissolution standard for aspirin, alumina, and magnesia tablets as contained in USP 23 at page 138.

(f) Aspirin, alumina, and magnesium oxide tablets. Aspirin in combination with alumina, and magnesium oxide in a tablet dosage form must meet the dissolution standard for aspirin, alumina, and magnesium tablets as contained in USP 23 at page 139.

(g) Aspirin effervescent tablets for oral solution. Aspirin effervescent tablets for oral solution must meet the dissolution standard for aspirin effervescent tablets for oral solution as contained in USP 23 at page 137.

(h) Buffered aspirin tablets. Buffered aspirin tablets must meet the dissolution standard for buffered aspirin tablets as contained in USP 23 at page 135.