| FDC date | State | City | Airport | FDC No. | SIAP |
|---|---|---|---|---|---|
| 08/30/99 | AR | LITTLE ROCK | ADAMS FIELD | 9/6600 | VOR/DME RNAV RWY 22R, AMDT 11... |
| 08/30/99 | CA | RAMONA | RAMONA | 9/6551 | VOR/DME OR GPS–A AMDT 1B... |
| 08/30/99 | CA | RAMONA | RAMONA | 9/6552 | GPS RWY 9 ORIG... |
| 08/30/99 | CA | SANTA YNEZ | SANTA YNEZ | 9/6553 | GPS–A ORIG–A... |
| 08/30/99 | CA | SANTA YNEZ | SANTA YNEZ | 9/6557 | VOR OR GPS–B AMDT 7B... |
| 08/30/99 | FL | LAKELAND | LAKELAND LINDER REGIONAL | 9/6592 | NDB OR GPS RWY 5, AMDT 2A... |
| 08/30/99 | FL | LAKELAND | LAKELAND LINDER REGIONAL | 9/6593 | ILS RWY 5, AMDT 5A... |
| 08/30/99 | FL | LAKELAND | LAKELAND LINDER REGIONAL | 9/6594 | VOR OR GPS RWY 27, AMDT 5A... |
| 08/30/99 | FL | LAKELAND | LAKELAND LINDER REGIONAL | 9/6595 | VOR OR GPS RWY 9, AMDT 2... |
| 08/30/99 | GUA | AGANA | GUAM INTL | 9/6555 | NDB/DME RWY 24R ORIG... |
| 08/30/99 | MA | HYANNIS | BARNSTABLE MUNI-BOARDMAN/ POLANDO FIELD. | 9/6581 | VOR OR GPS RWY 6 AMDT 7B... |
| 08/30/99 | MD | SALISBURY | SALISBURY-OCEAN CITY WICOMICO REGIONAL. | 9/6569 | VOR OR GPS RWY 32 AMDT 8A... |
| 08/30/99 | MN | LITTLE FALLS | LITTLE FALLS-MORRISON COUNTY | 9/6565 | NDB RWY 30 AMDT 6... |
| 08/30/99 | MN | LITTLE FALLS | LITTLE FALLS-MORRISON COUNTY | 9/6566 | GPS RWY 30 ORIG... |
| 08/30/99 | OR | ASTORIA | ASTORIA REGIONAL | 9/6591 | ILS RWY 26 AMDT 2... |
| 08/30/99 | OR | EUGENE | EUGENE/MAHLON SWEET FIELD | 9/6588 | NDB RWY 16 AMDT 29A... |
| 08/30/99 | OR | PORTLAND | PORTLAND INTL | 9/6585 | ILS RWY 28R AMDT 12... |
| 08/30/99 | OR | SALEM | MCNARY FIELD | 9/6587 | ILS RWY 31 AMDT 27A... |
| 08/30/99 | RI | PROVIDENCE | THEODORE FRANCIS GREEN STATE. | 9/6583 | GPS RWY 16 ORIG... |
| 08/30/99 | WA | MOSES LAKE | GRANT COUNTY INTL | 9/6582 | ILS RWY 32R, AMDT 19... |
| 08/30/99 | WA | MOSES LAKE | GRANT COUNTY INTL | 9/6584 | HI–IL/DME RWY 32R AMDT 1... |
| 08/30/99 | WA | MOSES LAKE | GRANT COUNTY INTL | 9/6586 | HI–VOR/DME OR TACAN RWY 32R, AMDT 1... |
| 08/30/99 | WA | MOSES LAKE | GRANT COUNTY INTL | 9/6589 | MLS RWY 32R, ORIG... |
| 08/30/99 | WA | SEATTLE | SEATTLE-TACOMA INTL | 9/6580 | ILS/DME RWY 34L, AMDT 1... |
| 08/30/99 | WY | TORRINGTON | TORRINGTON MUNI | 9/6560 | GPS RWY 28, ORIG... |
| 08/30/99 | WY | TORRINGTON | TORRINGTON MUNI | 9/6561 | GPS RWY 10, ORIG... |
| 08/30/99 | WY | TORRINGTON | TORRINGTON MUNI | 9/6562 | NDB RWY 28, AMDT 1... |
| 08/30/99 | WY | TORRINGTON | TORRINGTON MUNI | 9/6563 | NDB RWY 10, AMDT 1... |
| 08/31/99 | CA | FIREBAUGH | FIREBAUGH | 9/6637 | VOR/DME OR GPS–A, AMDT 2A... |
| 08/31/99 | DE | WILMINGTON | NEW CASTLE COUNTY | 9/6633 | GPS RWY 9 ORIG–A... |
| 08/31/99 | PA | BRADFORD | BRADFORD REGIONAL | 9/6625 | VOR/DME OR GPS RWY 14 AMDT 8A... |
| 08/31/99 | PA | FRANKLIN | VENAGO REGIONAL | 9/6626 | VOR OR GPS RWY 2 AMDT 3A... |
| 08/31/99 | PA | JOHNSTOWN | JOHNSTOWN-CAMBRIA COUNTY | 9/6629 | VOR/DME OR GPS RWY 15 AMDT 4A... |
| 08/31/99 | PA | STATE COLLEGE | UNIVERSITY PARK | 9/6627 | VOR/DME RNAV OR GPS RWY 6 AMDT 6A... |
| 08/31/99 | WV | MARTINSBURG | EASTERN WEST VIRGINIA REGIONAL/SHEPHERD FIELD. | 9/6639 | LOC/DME BC RWY 8 AMDT 5A... |

[FR Doc. 99–23726 Filed 9–13–99; 8:45 am]
**BILLING CODE 4910–13–M**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

### 21 CFR Part 343

**[Docket No. 77N–094A]**

## Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Final Rule for Professional Labeling of Aspirin, Buffered Aspirin, and Aspirin in Combination with Antacid Drug Products; Technical Amendments

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule; technical amendments.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the regulations for internal analgesic, antipyretic, and antirheumatic drug products for over-the-counter (OTC) use to correct inadvertent errors and to clarify the labeling for over-the-counter drug products written for health professionals.

**EFFECTIVE DATE:** The regulation is effective October 25, 1999.

**FOR FURTHER INFORMATION CONTACT:** Ida I. Yoder, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2222.

**SUPPLEMENTARY INFORMATION:** FDA has discovered that inadvertent errors were incorporated into the agency's regulations for internal analgesic, antipyretic, and antirheumatic drug products (21 CFR part 343), that published on October 23, 1998 (63 FR 56802). This document corrects those errors and clarifies the labeling for over-the-counter drug products written for health professionals. Publication of this document constitutes final action under the Administrative Procedure Act (5 U.S.C. 553). FDA has determined that notice and public comment are unnecessary because this amendment is nonsubstantive.

**List of Subjects in 21 CFR Part 343**

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 343 is amended as follows:

## PART 343—INTERNAL ANALGESIC, ANTIPYRETIC, AND ANTIRHEUMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 343 continues to read as follows:

**Authority:** 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

2. Section 343.80 is amended by revising paragraph (a)(1) to read as follows:

### § 343.80 Professional labeling.

(a) * * *

(1) The labeling contains the following prescribing information under the heading ''Comprehensive Prescribing Information'' and the subheadings ''Description,'' ''Clinical Pharmacology,'' ''Clinical Studies,'' ''Animal Toxicology,'' ''Indications and Usage,'' ''Contraindications,'' ''Warnings,'' ''Precautions,'' ''Adverse Reactions,'' ''Drug Abuse and Dependence,'' ''Overdosage,'' ''Dosage and Administration,'' and ''How Supplied'' in the exact language and the exact order provided as follows:

**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.

**CLINICAL PHARMACOLOGY**

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 cyclo-oxygenase 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 **Pharmacokinetics**—*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 75 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 **Overdosage**.)

*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 acyl 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 salicyluric 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 urine pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from < 5 percent to > 80 percent. Alkalinization of the urine is a key concept in the management of salicylate overdose. (See **Overdosage**.) Following therapeutic doses, approximately 10 percent is found excreted in the urine as salicylic acid, 75 percent as salicyluric acid, and 10 percent phenolic and 5 percent acyl glucuronides of salicylic acid.

Pharmacodynamics

Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A2. Nonacetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin $I_2$ (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

At higher doses aspirin is an effective anti-inflammatory agent, partially due to inhibition of inflammatory mediators via cyclo-oxygenase inhibition in peripheral tissues. In vitro studies suggest that other mediators of inflammation may also be suppressed by aspirin administration, although the precise mechanism of action has not been elucidated. It is this nonspecific suppression of cyclo-oxygenase activity in peripheral tissues following large doses that leads to its primary side effect of gastric irritation. (See **Adverse Reactions**.)

**CLINICAL STUDIES**

*Ischemic Stroke and Transient Ischemic Attack (TIA):* In clinical trials of subjects with TIA's due to fibrin platelet emboli or ischemic stroke, aspirin has been shown to significantly reduce the risk of the combined endpoint of stroke or death and the combined endpoint of TIA, stroke, or death by about 13–18 percent.

*Suspected Acute Myocardial Infarction (MI):* In a large, multi-center study of aspirin, streptokinase, and the combination of aspirin and streptokinase in 17,187 patients with suspected acute MI, aspirin treatment produced a 23-percent reduction in the risk of vascular mortality. Aspirin was also shown to have an additional benefit in patients given a thrombolytic agent.

*Prevention of Recurrent MI and Unstable Angina Pectoris:* These indications are supported by the results of six large, randomized, multi-center, placebo-controlled trials of predominantly male post-MI subjects and one randomized placebo-controlled study of men with unstable angina pectoris. Aspirin therapy in MI subjects was associated with a significant reduction (about 20 percent) in the risk of the combined endpoint of subsequent death and/or nonfatal reinfarction in these patients. In aspirin-treated unstable angina patients the event rate was reduced to 5 percent from the 10 percent rate in the placebo group.

*Chronic Stable Angina Pectoris:* In a randomized, multi-center, double-blind trial designed to assess the role of aspirin for prevention of MI in patients with chronic stable angina pectoris, aspirin significantly reduced the primary combined endpoint of nonfatal MI, fatal MI, and sudden death by 34 percent. The secondary endpoint for vascular events (first occurrence of MI, stroke, or vascular death) was also significantly reduced (32 percent).

*Revascularization Procedures:* Most patients who undergo coronary artery revascularization procedures have already had symptomatic coronary artery disease for which aspirin is indicated. Similarly, patients with lesions of the carotid bifurcation sufficient to require carotid endarterectomy are likely to have had a precedent event. Aspirin is recommended for patients who undergo revascularization procedures if there is a preexisting condition for which aspirin is already indicated.

*Rheumatologic Diseases:* In clinical studies in patients with rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis and osteoarthritis, aspirin has been shown to be effective in controlling various indices of clinical disease activity.

**ANIMAL TOXICOLOGY**

The acute oral 50 percent lethal dose in rats is about 1.5 g/kilogram (kg) and in mice 1.1 g/kg. Renal papillary necrosis and decreased urinary concentrating ability occur in rodents chronically administered high doses. Dose-dependent gastric mucosal injury occurs in rats and humans. Mammals may develop aspirin toxicosis associated with GI symptoms, circulatory effects, and central nervous system depression. (See **Overdosage**.)

**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), and Carotid Endarterectomy):* Aspirin is indicated in patients who have undergone revascularization procedures (i.e., CABG, PTCA, or carotid endarterectomy) when there is a preexisting condition for which aspirin is already indicated.

*Rheumatologic Disease Indications (Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Spondyloarthropathies, Osteoarthritis, and the Arthritis and Pleurisy of Systemic Lupus Erythematosus (SLE)):* Aspirin is indicated for the relief of the signs and symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondyloarthropathies, and arthritis and pleurisy associated with SLE.

**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.

*Peptic 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 hyponatremic and 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 0.5 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 with 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 200 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:* Dyspepsia, 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, bronchospasm, 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 indefinitely.

*CABG:* 325 mg daily starting 6 hours post-procedure. 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.

*Carotid Endarterectomy:* Doses of 80 mg once daily to 650 mg twice daily, started presurgery, are recommended. Continue therapy indefinitely.

*Rheumatoid Arthritis:* The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150–300 µg/mL. At high doses (i.e., plasma levels of greater than 200 µg/mL), the incidence of toxicity increases.

*Juvenile Rheumatoid Arthritis:* Initial dose is 90–130 mg/kg/day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150–300 µg/mL. At high doses (i.e., plasma levels of greater than 200 µg/mL), the incidence of toxicity increases.

*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 150–300 µg/mL. At high doses (i.e., plasma levels of greater than 200 mµ/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).

REV: October 23, 1998.

Dated: September 7, 1999.

**Margaret M. Dotzel,**

*Acting Associate Commissioner for Policy.*

[FR Doc. 99–23684 Filed 9–13–99; 8:45 am]

**BILLING CODE 4160–01–F**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

### 21 CFR Part 558

### New Animal Drugs for Use in Animal Feeds; Lasalocid and Virginiamycin

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of a new animal drug application (NADA) filed by Roche Vitamins, Inc. The NADA provides for