CHOLINE MAGNESIUM TRISALICYLATE - choline magnesium trisalicylate liquid

Silarx Pharmaceuticals, Inc

DESCRIPTION

Choline Magnesium Trisalicylate Liquid is a nonsteroidal, anti-inflammatory preparation containing choline magnesium trisalicylate which is freely soluble in water. The absolute structure of choline magnesium trisalicylate is not known at this time. Choline magnesium trisalicylate has a molecular formula of $C_{26}H_{29}O_{10}NMg$, a molecular weight of 539.8, and it may be represented in the solid form as:

Choline Magnesium Trisalicylate Liquid is a cherry-flavored liquid providing 500 mg salicylate content per teaspoonful (5 mL) for oral administration.

Inactive Ingredients: Each teaspoonful (5 mL) of Choline Magnesium Trisalicylate Liquid contains: caramel, carboxymethylcellulose sodium, edetate disodium, FD&C yellow no. 6, flavor, glycerin, methylparaben, potassium sorbate, sodium citrate, sorbic acid, sorbitol, and water.

CLINICAL PHARMACOLOGY

Choline Magnesium Trisalicylate Liquid contains salicylate with anti-inflammatory, analgesic and antipyretic action. On ingestion of Choline Magnesium Trisalicylate Liquid, the salicylate moiety is absorbed rapidly and reaches peak blood levels within an average of one to two hours after single dose of the liquid. The primary route of excretion is renal: the excretion products are chiefly the glycine and glucuronide conjugates. At higher serum salicylate concentrations, the glycine conjugation pathway becomes rapidly saturated. Thus, the slower glucuronide conjugation pathway becomes the rate limiting step for salicylate excretion. In addition, salicylate excreted in the bile as glucuronide conjugate may be reabsorbed. These factors account for the prolongation of salicylate half-life and the nonlinear increase in plasma salicylate level as the salicylate dose is increased. The serum concentration of salicylate is increased by conditions that decrease glomerular filtration rate or proximal tubular secretion.

Unlike <u>aspirin</u> and certain other non-steroidal anti-inflammatory agents, such as arylpropionic acid derivatives and arylacetic acid derivatives, choline magnesium trisalicylate at therapeutic dosage levels does not affect platelet aggregation, as shown by in-vitro and in-vivo studies.

INDICATIONS AND USAGE

Osteoarthritis, Rheumatoid Arthritis and Acute Painful Shoulder: Salicylates are considered the base therapy of choice in the arthritides; and choline magnesium trisalicylate preparation is indicated for the relief of the signs and symptoms of rheumatoid arthritis, osteoarthritis and other arthritides. Choline Magnesium Trisalicylate Liquid is indicated in the long-term management of these diseases and especially in the acute flare of rheumatoid arthritis. Choline Magnesium Trisalicylate Liquid is also indicated for the treatment of acute painful shoulder.

Choline Magnesium Trisalicylate Liquid is effective and generally well tolerated, and is logical choice whenever salicylate treatment is indicated. It is particularly suitable when a once-a-day or b.i.d. dosage regimen is important to patient compliance; when gastrointestinal intolerance to aspirin is encountered; when gastrointestinal microbleeding or hematologic effects of aspirin are considered a patient hazard; and when interference (or the risk of interference) with normal platelet function by aspirin or by propionic acid derivatives is considered to be clinically undesirable. Use of Choline Magnesium Trisalicylate Liquid is appropriate when a liquid dosage form is preferred, as in the elderly patient.

The efficacy of Choline Magnesium Trisalicylate Liquid has not been studied in those patients who are designated by the American Rheumatism Association as belonging in

Functional Class IV (incapacitated, largely or wholly bedridden or confined to a wheelchair, with little or no self-care).

Analgesic and Antipyretic Action: Choline Magnesium Trisalicylate Liquid is also indicated for the relief of mild to moderate pain and for antipyresis.

Pediatric Use

In children, Choline Magnesium Trisalicylate Liquid is indicated for conditions requiring anti-inflammatory or analgesic action-such as juvenile rheumatoid arthritis and other appropriate conditions.

CONTRAINDICATIONS

Patients who are hypersensitive to non-acetylated salicylates should not take Choline Magnesium Trisalicylate Liquid.

WARNINGS

Reye Syndrome is a rare but serious disease which may develop in children and teenagers who have chicken pox, influenza, or flu symptoms. While the cause of Reye Syndrome is unknown, some studies suggest a possible association between the development of Reye Syndrome and the use of medicines containing acetylated salicylates or aspirin. Choline Magnesium Trisalicylate Liquid is a combination of choline salicylate and magnesium salicylate which are nonacetylated salicylates, and there have been no reported cases

associating Choline Magnesium Trisalicylate Liquid with Reye Syndrome. Nevertheless, Choline Magnesium Trisalicylate Liquid, as a salicylate-containing product, is not recommended for use in children and teenagers with chicken pox, influenza or flu symptoms. The FDA has determined that routine heavy alcohol use (three or more alcoholic drinks every day), in combination with analgesic/antipyretic drug products containing NSAID ingredients (including choline and magnesium salicylates), increases the risk of adverse GI events, including stomach bleeding.

PRECAUTIONS

General Precautions

As with other salicylates and non-steroidal anti-inflammatory drugs, Choline Magnesium Trisalicylate Liquid should be used with caution in patients with acute or chronic renal insufficiency, with acute or chronic hepatic dysfunction, or with gastritis or peptic ulcer disease. Although reports exist of cross reactivity, including bronchospasm, with the use of non-acetylated salicylate products in aspirin-sensitive patients, Choline Magnesium Trisalicylate Liquid was found to be well tolerated with regard to pulmonary function and respiratory symptoms when these parameters were monitored in a group of documented aspirin-sensitive asthmatics dosed with Choline Magnesium Trisalicylate Liquid in both controlled and open label studies.

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Concurrent use of other salicylate-containing products and Choline Magnesium Trisalicylate Liquid can lead to an increase in plasma salicylate concentration and may result in potentially toxic salicylate levels.

Laboratory Tests

Plasma salicylate levels can be periodically assessed during treatment with Choline Magnesium Trisalicylate Liquid to determine whether a therapeutically effective antiinflammatory concentration of 15 to 30 mg/100 mL (150-300 micrograms/mL) is being maintained. Manifestations of systemic salicylate intoxication are usually not seen until the concentration exceeds 30 mg/100 mL. However, such tests rarely differentiate between the active free and inactive protein bound salicylate components. Since protein binding of salicylate is affected by age, nutritional status, competitive binding of other drugs, and underlying disease (e.g., rheumatoid arthritis), plasma salicylate level determinations may not always accurately reflect efficacious or toxic levels of active free salicylate. Acidification of the urine can significantly diminish the renal clearance of salicylate and increase plasma salicylate concentrations.

Drug Interactions

Foods and drugs that alter urine pH may affect renal clearance of salicylate and plasma salicylate concentrations. Raising urine pH, as with chronic antacid use, can enhance renal salicylate clearance and diminish plasma salicylate concentration; urine acidification can decrease urinary salicylate excretion and increase plasma levels.

When salicylate drug products are concurrently dosed with other plasma protein bound drug products, adverse effects may result. Although Choline Magnesium Trisalicylate Liquid is a rational choice for anti-inflammatory and analgesic therapy in patients on oral anticoagulants due to their demonstrated lack of effect in vivo and in vitro on platelet aggregation, bleeding time, platelet count, prothrombin time, and serum thromboxane B2 generation¹⁻⁷, the potential exists for increased levels of unbound warfarin with their concurrent use. Prothrombin time should be closely monitored and warfarin dose appropriately adjusted when therapy with Choline Magnesium Trisalicylate Liquid is initiated. The effect of Choline Magnesium Trisalicylate Liquid on blood prothrombin levels has not been established. Salicylates may increase the therapeutic as well as toxic effects of methotrexate, particularly when administered in chemotherapeutic doses, by inhibition of renal methotrexate excretion and by displacement of plasma protein bound methotrexate. Caution should be exercised in administering Choline Magnesium Trisalicylate Liquid to rheumatoid arthritis patients on methotrexate. When sulfonylurea oral hypoglycemic agents are co-administered with salicylates, the hypoglycemic effect may be enhanced via increased insulin secretion or by displacement of sulfonylurea agents from binding sites. Insulin-treated diabetics on high doses of salicylates should also be closely monitored for a similar hypoglycemic response. Other drugs with which salicylate competes for protein binding sites, and whose plasma concentration or free fraction may be altered by concurrent salicylate administration, include the following: phenytoin, valproic acid, and carbonic anhydrase inhibitors.

The efficacy of uricosuric agents may be decreased when administered with salicylate products. Although low doses of salicylate (1 to 2 grams per day) have been reported to decrease urate excretion and elevate plasma urate concentrations, intermediate doses (2 to 3 grams per day) usually do not alter urate excretion. Larger salicylate doses (over 5 grams per day) can induce uricosuria and lower plasma urate levels.

Corticosteroids can reduce plasma salicylate levels by increasing renal elimination and perhaps by also stimulating hepatic metabolism of salicylates. By monitoring plasma salicylate levels, salicylate dosage may be titrated to accommodate changes in corticosteroid dose or to avoid salicylate toxicity during corticosteroid taper.

Drug/Laboratory Test Interactions

Free T4 values may be increased in patients on salicylate drug products due to competitive plasma protein binding; a concurrent decrease in total plasma T4 may be observed. Thyroid function is not affected.

Carcinogenesis

No long-term animal studies have been performed with Choline Magnesium Trisalicylate Liquid to evaluate its carcinogenic potential.

Use in Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Choline Magnesium Trisalicylate Liquid. It is also not known whether Choline Magnesium Trisalicylate Liquid can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Choline Magnesium Trisalicylate Liquid should be given to a pregnant woman only if clearly needed. Because of the known effect of other salicylate drug products on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided.

Labor and Delivery

The effects of Choline Magnesium Trisalicylate Liquid on labor and delivery in pregnant women are unknown. Since prolonged gestation and prolonged labor due to

prostaglandin inhibition have been reported with the use of other salicylate products, the use of Choline Magnesium Trisalicylate Liquid near term is not recommended. Other salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms and with perinatal mortality.

Nursing Mothers

Salicylate is excreted in human milk. Peak milk salicylate levels are delayed, occurring as long as 9 to 12 hours post dose, and the milk: plasma ratio has been reported to be as high as 0.34. Because of the potential for significant salicylate absorption by the nursing infant, caution should be exercised when Choline Magnesium Trisalicylate Liquid is administered to a nursing woman.

Geriatric Use

The elderly may be prone to more side effects from salicylates than younger patients due to an age-related decline in renal clearance and/or increased use of concomitant medication. The elderly are more likely than younger patients to be taking a number of medications, some of which may affect the plasma protein binding of salicylate and thus increase the amount of free salicylate.

ADVERSE REACTIONS

The most frequent adverse reactions observed with Choline Magnesium Trisalicylate Liquid in clinical trials⁷⁻¹² are tinnitus and gastrointestinal complaints (including nausea, vomiting, gastric upset, indigestion, heartburn, diarrhea, constipation and epigastric pain). These occur in less than twenty percent (20%) of patients. Should tinnitus develop, reduction of daily dosage is recommended until the tinnitus is resolved. Less frequent adverse reactions, occurring in less than two percent (2%) of patients, are: hearing impairment, headache, lightheadedness, dizziness, drowsiness, and lethargy. Adverse reactions occurring in less than one percent (1%) of patients, are: gastric ulceration, positive fecal occult blood, elevation in serum BUN and creatinine, rash, pruritus, anorexia, weight gain, edema, epistaxis and dysgeusia.

Spontaneous reporting has yielded isolated or rare reports of the following adverse experiences: duodenal ulceration, elevated hepatic transaminases, hepatitis, esophagitis,

asthma, erythema multiforme, urticaria, ecchymoses, irreversible hearing loss and/or tinnitus, mental confusion and hallucinations.

DRUG ABUSE AND DEPENDENCE

Drug abuse and dependence have not been reported with Choline Magnesium Trisalicylate Liquid.

OVERDOSAGE

Death in adults has been reported following ingestion of doses from 10 to 30 grams of salicylate; however, larger doses have been taken without resulting fatality.

Symptoms: Salicylate intoxication, known as salicylism, may occur with large doses or extended therapy. Common symptoms of salicylism include headache, dizziness, tinnitus, hearing impairment, confusion, drowsiness, sweating, vomiting, diarrhea, and hyperventilation. A more severe degree of salicylate intoxication can lead to CNS disturbances, alteration in electrolyte balance, respiratory and metabolic acidosis, hyperthermia, and dehydration.

Treatment: Reduction of further absorption of salicylate from the gastrointestinal tract can be achieved via emesis, gastric lavage, use of activated charcoal, or a combination of the above. Appropriate I.V. fluids should be administered to correct dehydration, electrolyte imbalance, and acidosis and to maintain adequate renal function. To accelerate salicylate excretion, forced diuresis with alkalinizing solution is recommended. In extreme cases, peritoneal dialysis or hemodialysis should be considered for effective salicylate removal.

DOSAGE AND ADMINISTRATION

Adults

In rheumatoid arthritis, osteoarthritis, the more severe arthritides, and acute painful shoulder, the recommended starting dosage is 1500 mg given b.i.d. Some patients may be treated with 3000 mg given once per day (h.s.). Dosage should be adjusted in accordance with the patient's response. In patients with renal dysfunction, monitor salicylate levels and adjust dose accordingly.

Elderly

In the elderly patient, a daily dosage of 2250 mg given as 750 mg t.i.d. may be efficacious and well tolerated. Dosage should be adjusted in accordance with the patient's

response. In patients with renal dysfunction, monitor salicylate levels and adjust dose accordingly.

For mild to moderate pain or for antipyresis, the usual dosage is 2000 mg to 3000 mg daily in divided doses (b.i.d.). Based on patient response or salicylate blood levels, dosage may be adjusted to achieve optimum therapeutic effect. Salicylate blood levels should be in the range of 15 to 30 mg/100 mL for anti-inflammatory effect and 5 to 15 mg/100 mL for analgesia and antipyresis.

If the physician prefers, the recommended daily dosage may be administered on a t.i.d. schedule.

As with other therapeutic agents, individual dosage adjustment is advisable, and a number of patients may require higher or lower dosages than those recommended. Certain patients require 2 to 3 weeks of therapy for optimal effect.

Children

Usual daily dose for children for anti-inflammatory or analgesic action: Choline Magnesium Trisalicylate Liquid, 50 mg/kg/day.

Weight (kg)	Total daily dose
12 - 13	500 mg
14 - 17	750 mg
18 - 22	1000 mg
23 - 27	1250 mg
28 - 32	1500 mg
33 - 37	1750 mg

Total daily doses should be administered in divided doses (b.i.d.). The dose of Choline Magnesium Trisalicylate Liquid is calculated as the total daily dose of 50 mg/kg/day for children of 37 kg body weight or less and 2250 mg/day for heavier children. Choline Magnesium Trisalicylate Liquid is available for greater convenience in treating younger patients and those adult patients unable to swallow a solid dosage form. Choline Magnesium Trisalicylate Liquid may be mixed with fruit juices just before ingestion.

HOW SUPPLIED

Choline Magnesium Trisalicylate Liquid is supplied in bottles of 240 mL.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

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Silarx Pharmaceutical, Inc.

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