PRESCRIBING INFORMATION

ACETAZONE FORTE

chlorzoxazone and acetaminophen, USP

Tablets

250 mg / 300 mg

MUSCLE RELAXANT & PAIN RELIEVER

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PRESCRIBING INFORMATION

ACETAZONE FORTE

Chlorzoxazone Acetaminophen USP tablets

Muscle relaxant - Analgesic

ACTION AND CLINICAL PHARMACOLOGY

Acetazone Forte tablets combine the muscle-relaxant effect of chlorzoxazone with acetaminophen, a well known analgesic.

Chlorzoxazone is a centrally-acting agent for painful musculoskeletal conditions. Data available from animal experiments, as well as human study, indicate that chlorzoxazone acts primarily at the level of the spinal cord and subcortical areas of the brain where it inhibits multisynaptic reflex arcs involved in producing and maintaining skeletal muscle spasm of varied etiology. The clinical result is a reduction of the skeletal muscle spasm with relief of pain and increased mobility of the involved muscles. Blood levels of chlorzoxazone can be detected in humans during the first 30 minutes after oral administration and peak levels may be reached in about 1 to 2 hours. Chlorzoxazone is rapidly metabolized and is excreted in the urine, primarily in a conjugated form as the glucuronide. Less than 1% of a dose of chlorzoxazone is excreted unchanged in the urine in 24 hours.

Acetaminophen provides analgesic action to supplement that which results secondarily from muscle relaxation. Acetaminophen is rapidly absorbed after oral administration, with peak plasma levels occurring in 1 to 2 hours. After 8 hours, only negligible amounts remain in the blood. Only 4% is excreted unchanged; 85% of the ingested dose is recovered in the urine in conjugated form as the glucuronide. Acetaminophen is distributed throughout most tissues of the body. Acetaminophen is metabolized primarily

in the liver. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

The mode of action of chlorzoxazone has not been clearly identified, but may be related to its sedative properties. Chlorzoxazone does not directly relax tense skeletal muscles in man.

Following oral administration chlorzoxazone in combination with acetaminophen both drugs are rapidly absorbed. Mean drug plasma concentrations reach a peak level in the majority of subjects in 45 to 90 minutes.

The plasma elimination half-life is about 1 hour for chlorzoxazone and ranges from 1.5 to 3.5 hours for acetaminophen.

Metabolism is rapid, the principle metabolites are conjugates of glucuronic acid which are excreted primarily in the urine. Less than 1% of an administered dose of chlorzoxazone and less than 4% of an administered dose of acetaminophen is excreted unchanged in the urine in 24 hours. Only traces of unchanged drug are excreted through the bile into the feces.

INDICATIONS

As an adjunct to rest, physical therapy and other measures for the relief of discomfort associated with acute musculoskeletal conditions. Such conditions may include skeletal muscle spasm and pain associated with sprains, strains and other traumatic muscle injuries; myalgias; arthritides; low back pain; tension headache; torticollis; fibrositis; spondylitis; and cervical root and disc syndromes.

CONTRAINDICATIONS

Hypersensitivity to the components, hepatic impairment and acute porphyria.

PRECAUTIONS

As with any other nonprescription analgesic drug, physicians should be cognizant of and supervise the use of acetaminophen in patients with alcoholism, serious kidney or serious liver disease. Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive doses of acetaminophen, although reports of this event are rare. Reports usually involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Physicians should alert their patients who regularly consume large amounts of alcohol not to exceed the recommended doses of acetaminophen.

Patients should be counseled to consult a physician if redness or swelling is present in an area of pain, if symptoms do not improve or if they worsen, or if new symptoms such as high fever, rash, itching, or persistent headache occur, as these may be signs of a condition which requires medical attention.

Acetaminophen should not be taken for pain for more than 5 days unless directed by a physician.

Pregnancy and Lactation:

As with any drug, patients who are pregnant or nursing a baby should consult a physician before taking this product.

Do not use with other products containing acetaminophen, salicylates or any other pain or fever medicine.

Keep out of the reach of children.

Use with caution in patients with known allergies or with a history of allergic reactions to drugs. If a sensitivity reaction occurs such as urticaria, redness, or itching of the skin, the drug should be stopped.

There have been reports of liver damage associated with the use of chlorzoxazone-containing products. If any symptoms suggestive of liver dysfunction are observed, the drug should be discontinued.

Acetazone Forte should be used with caution in patients with severe impairment of renal function.

Occupational hazards:

Drowsiness can occur with the use of Acetazone Forte. Patients using this drug should be cautioned about driving a car or operating potentially hazardous machinery if they become drowsy or show impaired mental or physical abilities while taking this medication.

Drug interactions:

Patients receiving antipsychotics, antianxiety agents or other CNS depressants (including alcohol) concomitantly with this drug may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Avoid consumption of alcohol while using this product.

Pregnancy:

Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation:

Chlorzoxazone and acetaminophen is not recommended during lactation because safety in nursing mothers has not been established. It is not known if chlorzoxazone is excreted in breast milk. Acetaminophen passes into breast milk but is not likely to have an adverse effect on the infant at therapeutic doses.

Children:

Because safety and effectiveness have not been established in children such use is not recommended.

ADVERSE REACTIONS

The classic gastrointestinal irritation with NSAIDs, including ASA, does not occur with acetaminophen. Sensitivity reactions are rare and may manifest as rash or urticaria. Cross-reactivity in ASA-sensitive persons has been rarely reported. If sensitivity is suspected, discontinue use of the drug.

Patients who concomitantly medicate with warfarin-type anticoagulants and regular doses of acetaminophen have occasionally been reported to have unforeseen elevations in their INR. Physicians should be cognizant of this potential interaction and monitor the INR in such patients closely while therapy is established.

Gastrointestinal:

Occasionally patients may develop gastrointestinal disturbances and abdominal pain. It is possible in rare instances that chlorzoxazone may have been associated with gastrointestinal bleeding.

CNS:

Drowsiness, dizziness, lightheadedness, malaise, or overstimulation may be noted by an occasional patient.

Allergic:

Rarely, allergic-type skin rashes, petechiae, or ecchymoses may develop during treatment. Angioneurotic edema or anaphylactic reactions are extremely rare.

Renal toxicity:

There is no evidence that this medicine will cause renal damage. Rarely, a patient may note discoloration of the urine resulting from a phenolic metabolite of chlorzoxazone. This finding is of no known clinical significance.

Hepatotoxicity:

Serious, including fatal, hepatocellular toxicity has been reported rarely in patients receiving chlorzoxazone. The mechanism is unknown but appears to be idiosyncratic and unpredictable. Factors predisposing patients to this rare event are not known. Patients should be instructed to report early signs and/or symptoms of hepatotoxicity such as fever, rash, anorexia, nausea, vomiting, fatigue, right upper quadrant pain, dark urine, or jaundice. Chlorzoxazone should be discontinued immediately and a physician consulted if any of these signs or symptoms develop. Chlorzoxazone use should also be discontinued if a patient develops abnormal liver enzymes (e.g., AST, ALT, alkaline phosphatase or bilirubin).

In a controlled multidose clinical trial with chlorzoxazone 500 mg, the following adverse events occurred in $\geq$1% of patients receiving chlorzoxazone or occurred in < 1% of patients but resulted in patient withdrawal from the study and were considered possibly, probably or definitely related to chlorzoxazone.

Body as a Whole:

Asthenia (2%), body pain, edema.

CNS:

Anxiety, dizziness (6%), drowsiness (9%), headache (5%), nervousness, paresthesia, vertigo.

Gastrointestinal:

Abnormal pain, anorexia, diarrhea (2%), dyspepsia (1%), flatulence, melena, nausea (3%).

Skin:

pruritus, rash, skin discoloration.

Urogenital:

Polyuria.

The following adverse reports occurred with a frequency of <1% and the relationship to chlorzoxazone remains undetermined; chills, tachycardia, vasodilation, abnormal thinking, confusion, depression, emotional liability, hypotonia, insomnia, constipation, dry mouth, thirst, vomiting, cough increase, dyspnea, flu symptoms, rhinitis, sweating, increased urinary frequency, menorrhagia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acetaminophen: Typical Toxidrome: Significant overdoses of acetaminophen may result in potentially fatal hepatotoxicity. The physician should be mindful that there is no early presentation that is pathoneumonic for the overdose. A high degree of clinical suspicion must always be maintained.

Due to the wide availability of acetaminophen, it is commonly involved in single and mixed drug overdose situations and the practitioner should have a low threshold for screening for its presence in a patient's serum. Acute toxicity after single dose overdoses of acetaminophen can be anticipated when the overdose exceeds 150 mg/kg. Chronic alcohol abusers, cachectic individuals, and persons taking pharmacologic inducers of the hepatic P450 microsomal enzyme system may be at risk with lower exposures.

There have been rare reports of chronic intoxication in persons consuming in excess of 150 mg/kg of acetaminophen daily for several days.

Specific Antidote: NAC (N-acetylcysteine) administered by either the i.v. or the oral route is known to be a highly effective antidote for acetaminophen poisoning. It is mot effective when administered within 8 hours of a significant overdose buy reports have indicated benefits to treatment initiated well beyond this time period. It is imperative to administer the antidote as early as possible in the time course of acute intoxication to reap the full benefits of the antidote's protective effects.

General Management:

When the possibility of acetaminophen overdose exists, treatment should begin immediately and include appropriate decontamination of the gastrointestinal tract, proper supportive care, careful assessment of appropriately timed serum acetaminophen estimations evaluated against the Mattew-Rumack nomogram, timely administration of NAC as required and appropriate follow-up care. Physicians unfamiliar with the current management of acetaminophen overdose should consult with a Poison Control Centre immediately. Telephone numbers for local Poison Control Centres are available in the local phone directory.

Delays in initiation of appropriate therapy may jeopardize the patient's chances for a full recovery.

Chlorzoxazone: Typical Toxidrome: extreme weakness (voluntary muscles), CNS depression, labored breathing.

Specific antidote: none

General Management: stabilize the patient (A, B, C's), undertake appropriate gastrointestinal tract decontamination procedures, initiate supportive care, consult with

a Regional Poison Control Centre regarding ongoing management, and arrange for appropriate follow-up care.

DOSAGE AND ADMINISTRATION

Adults: (12 years of age and older) 2 tablets 4 times a day. It is hazardous to exceed 8 tablets per day.

AVAILABILITY OF DOSAGE FORMS

Each round, green uncoated biplane tablet with beveled edges, imprinted "rph" on one side and single scored on the other side, contains: chlorzoxazone USP 250 mg and acetaminophen USP 300 mg. Non-medicinal ingredients in alphabetical order: Corn starch, crospovidone, D&C yellow #10 aluminum lake, FD&C blue #1 aluminum lake, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, sodium benzoate and sodium docusate, sodium croscarmellose, and stearic acid. Bottles of 100 and blister packs of 30.

Keep the bottle tightly closed. Protect from light. Store at room temperature.

PHARMACEUTICAL INFORMATION

CHLORZOXAZONE

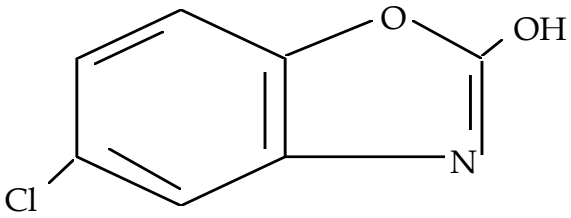
Chemical name: 5-chloro-2(3H)-benzoxazolone

Molecular formula: $C_7H_4Cl\ NO_2$

C 49.58%,H 2.38%,C l20.91%

N 8.26%, O 18.87%

Chemical structure:



Molecular weight: 169.58

Physical form: Crystals from acetone.

Solubility: Sparingly soluble in water, soluble in methanol, ethanol, isopropanol. Freely soluble in aqueous solutions of alkali hydroxides and ammonia.

Melting point: 191 - 191.5°C.

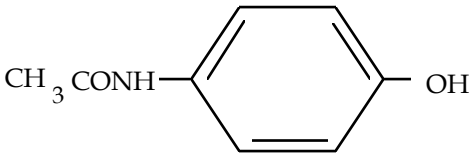
ACETAMINOPHEN

Chemical name: N-(4-Hydroxyphenyl) acetamide

Molecular formula: $C_8H_9NO_2$

C 63.56%, H 6.00%, N 9.27%, O 21.17%

Chemical structure:



Molecular weight: 151.16

Physical form: Large monoclinic prisms from water.

Solubility: Very slightly soluble in cold water, considerably more soluble in hot water. Soluble in methanol, ethanol, dimethylformamide, ethylene dichloride, acetone, ethyl acetate. Slightly soluble in ether. Practically insoluble in petroleum ether, pentane and benzene.

Melting point: 169 - 170.5°C.