

NSAID-Related Hepatotoxicity Rose Dramatically

BY BRUCE JANCIN
Denver Bureau

PARIS — Serious liver toxicity associated with the use of nonsteroidal anti-inflammatory drugs showed a sevenfold jump in incidence in a recent 10-year period in California.

The explanation for this alarming trend is speculative, but one key factor might be the steady growth in concomitant use of other potentially hepatotoxic drugs, such

as statins. Dr. Gurkirpal Singh observed at the annual European Congress of Rheumatology.

Another potential contributing factor could be the background rise in nonalcoholic fatty liver disease, added Dr. Singh of Stanford (Calif.) University.

Dr. Singh analyzed 1995-2005 data from MediCal, California's Medicaid program, which covers more than 7 million patients per year. Among 1.6 million MediCal participants with more than 3 million person-

years of NSAID use, there were 1,648 cases of serious liver toxicity (defined by a blinded adjudication panel comprising three hepatologists as hospitalization for hepatitis, acute liver failure, jaundice, hepatorenal syndrome, or hepatic coma). Cases of alcohol-related liver injury and viral hepatitis were excluded.

The overall incidence of serious liver toxicity associated with NSAID use was 55 cases per 100,000 person-years of exposure. The rate increased steadily from 22.9

cases per 100,000 person-years in 1995 to 142.4 in 2005. The fatality rate was 12.2%.

The incidence of acute liver failure climbed from 3.1 cases per 100,000 years of NSAID exposure in 1995 to 17.8 per 100,000 person-years in 2005.

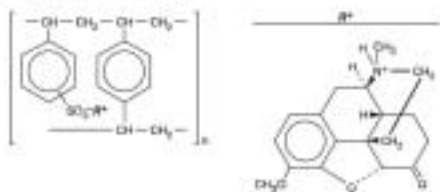
Dr. Singh recommended careful monitoring with periodic liver function tests in chronic NSAID users, particularly in those taking other potentially hepatotoxic drugs or having risk factors for fatty liver or other liver disorders. ■

Tussionex® Pennkinetic® (hydrocodone polistirex and chlorpheniramine polistirex) Extended-Release Suspension

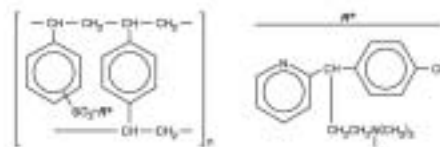
Rx Only
Rev. 01/2008 1E
T11186-0308 1E

DESCRIPTION: Each teaspoonful (5 mL) of TUSSIONEX Pennkinetic Extended-Release Suspension contains hydrocodone polistirex equivalent to 10 mg of hydrocodone bitartrate and chlorpheniramine polistirex equivalent to 8 mg of chlorpheniramine maleate. TUSSIONEX Pennkinetic Extended-Release Suspension provides up to 12-hour relief per dose. Hydrocodone is a centrally acting narcotic analgesic. Chlorpheniramine is an antihistamine. TUSSIONEX Pennkinetic Extended-Release Suspension is for oral use only.

Hydrocodone Polistirex: Sulfonated styrene-divinylbenzene copolymer complex with 4,5α-epoxy-3-methyl-17-methylmorphine-6-ene.



Chlorpheniramine Polistirex: Sulfonated styrene-divinylbenzene copolymer complex with 2-[p-chloro-α-[2-(dimethylamino)ethyl]benzyl]pyridine.



Inactive Ingredients: Acacia, D&C Yellow No. 11, ethylcellulose, FD&C Yellow No. 4, flavor, high fructose corn syrup, methylparaben, polyethylene glycol 3350, polybutyl acrylate, polybutyl methacrylate, propylene glycol, propylparaben, purified water, sucrose, vegetable oil, xanthan gum.

CLINICAL PHARMACOLOGY: Hydrocodone is a semisynthetic narcotic analgesic and anesthetic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone, like other opiate derivatives, will depress respiration. The effects of hydrocodone in therapeutic doses on the cardiovascular system are insignificant. Hydrocodone can produce miosis, euphoria, and physical and psychological dependence.

Chlorpheniramine is an antihistamine drug (H₁ receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents histamine from dilating capillaries and causing edema of the respiratory mucosa.

Hydrocodone release from TUSSIONEX Pennkinetic Extended-Release Suspension is controlled by the Pennkinetic System, an extended-release drug delivery system, which contains an ion-exchange polymer matrix with a diffusion rate limiting permeable coating. Chlorpheniramine release is prolonged by use of an ion-exchange polymer system.

Following multiple dosing with TUSSIONEX Pennkinetic Extended-Release Suspension, hydrocodone mean (S.D.) peak plasma concentrations of 22.8 (5.9) ng/mL, occurred at 3.4 hours. Chlorpheniramine mean (S.D.) peak plasma concentrations of 58.4 (14.7) ng/mL, occurred at 6.3 hours following multiple dosing. Peak plasma levels obtained with an immediate-release syrup occurred at approximately 1.5 hours for hydrocodone and 2.8 hours for chlorpheniramine. The plasma half-lives of hydrocodone and chlorpheniramine have been reported to be approximately 4 and 16 hours, respectively.

INDICATIONS AND USAGE: TUSSIONEX Pennkinetic Extended-Release Suspension is indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and older.

CONTRAINDICATIONS: TUSSIONEX Pennkinetic Extended-Release Suspension is contraindicated in patients with a known allergy or sensitivity to hydrocodone or chlorpheniramine.

The use of TUSSIONEX Pennkinetic Extended-Release Suspension is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression.

WARNINGS: Respiratory Depression: As with all narcotics, TUSSIONEX Pennkinetic Extended-Release Suspension produces dose-related respiratory depression by directly acting on brain stem respiratory centers. Hydrocodone affects the center that controls respiratory rhythm and may produce irregular and periodic breathing. Caution should be exercised when TUSSIONEX Pennkinetic Extended-Release Suspension is used postoperatively and in patients with pulmonary disease, or whenever ventilatory function is depressed. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated (see DOSAGE).

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions, which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Obstructive Bowel Disease: Chronic use of narcotics may result in obstructive bowel disease especially in patients with underlying intestinal motility disorder.

Pediatric Use: The use of TUSSIONEX Pennkinetic Extended-Release Suspension is contraindicated in children less than 6 years of age (see CONTRAINDICATIONS).

In pediatric patients, as well as adults, the respiratory center is sensitive to the depressant action of narcotic cough suppressants in a dose-dependent manner. Caution should be exercised when administering TUSSIONEX Pennkinetic Extended-Release Suspension to pediatric patients 6 years of age and older. Overdose or concomitant administration of TUSSIONEX Pennkinetic Extended-Release Suspension with other respiratory depressants may increase the risk of respiratory depression in pediatric patients. Benefit to risk ratio should be carefully considered, especially in pediatric patients with respiratory embarrassment (e.g., croup) (see PRECAUTIONS).

PRECAUTIONS: General: Caution is advised when prescribing this drug to patients with narrow-angle glaucoma, asthma, or prostatic hypertrophy.

Special Risk Patients: As with any narcotic agent, TUSSIONEX Pennkinetic Extended-Release Suspension should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Information for Patients: As with all narcotics, TUSSIONEX Pennkinetic Extended-Release Suspension may produce marked drowsiness and impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly. TUSSIONEX Pennkinetic Extended-Release Suspension must not be diluted with fluids or mixed with other drugs as this may alter the resin-binding and change the absorption rate, possibly increasing the toxicity.

Patients should be advised to measure TUSSIONEX Pennkinetic Extended-Release Suspension with an accurate measuring device. A household teaspoon is not an accurate measuring device and could lead to overdose, especially when a half a teaspoon is measured. A pharmacist can recommend an appropriate measuring device and can provide instructions for measuring the correct dose.

Shake well before using.

Keep out of the reach of children.

Cough Relief: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when TUSSIONEX Pennkinetic Extended-Release Suspension is used postoperatively, and in patients with pulmonary disease.

Drug Interactions: Patients receiving narcotics, anticholinergics, antidepressants, anxiolytic agents, or other CNS depressants (including alcohol) concomitantly with TUSSIONEX Pennkinetic Extended-Release Suspension may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

The concurrent use of other anticholinergics with hydrocodone may produce anticholinergic effects.

Contraception, Mutagenesis, Impairment of Fertility: Contraception, mutagenicity, and reproductive studies have not been conducted with TUSSIONEX Pennkinetic Extended-Release Suspension.

Pregnancy: Teratogenic Effects - Pregnancy Category C

Hydrocodone has been shown to be teratogenic in humans when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. TUSSIONEX Pennkinetic Extended-Release Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Neonatal Effects: Babies born to mothers who have been taking opiates regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of these symptoms does not always correlate with the duration of maternal opioid use or dose.

Labor and Delivery: As with all narcotics, administration of TUSSIONEX Pennkinetic Extended-Release Suspension to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TUSSIONEX Pennkinetic Extended-Release Suspension, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The use of TUSSIONEX Pennkinetic Extended-Release Suspension is contraindicated in children less than 6 years of age (see CONTRAINDICATIONS and ADVERSE REACTIONS, Respiratory, Thoracic and Mediastinal Disorders).

TUSSIONEX Pennkinetic Extended-Release Suspension should be used with caution in pediatric patients 6 years of age and older (see WARNINGS, Pediatric Use).

Geriatric Use: Clinical studies of TUSSIONEX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS: Gastrointestinal Disorders: Nausea and vomiting may occur; they are more frequent in ambulatory than in recumbent patients. Prolonged administration of TUSSIONEX Pennkinetic Extended-Release Suspension may produce constipation.

General Disorders and Administration Site Conditions: Drowsiness.

Nervous System Disorders: Dizziness, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, euphoria, dizziness, psychic dependence, mood changes.

Respiratory, Thoracic and Mediastinal Disorders: Dryness of the pharynx, occasional tightness of the chest, and respiratory depression (see CONTRAINDICATIONS).

TUSSIONEX Pennkinetic Extended-Release Suspension may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSSAGE). Use of TUSSIONEX Pennkinetic Extended-Release Suspension in children less than 6 years of age has been associated with fatal respiratory depression. Overdose with TUSSIONEX Pennkinetic Extended-Release Suspension in children 6 years of age and older, in adolescents, and in adults has been associated with fatal respiratory depression.

Skin and Subcutaneous Tissue Disorders: Rash, pruritus.

DRUG ABUSE AND DEPENDENCE: TUSSIONEX Pennkinetic Extended-Release Suspension is a Schedule III narcotic. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics; however, TUSSIONEX Pennkinetic Extended-Release Suspension should be prescribed and administered with caution. However, psychic dependence is unlikely to develop with TUSSIONEX Pennkinetic Extended-Release Suspension is used for a short time for the treatment of cough. Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, occurs in clinically significant proportions only after several weeks of continued and narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy.

OVERDOSSAGE: Signs and Symptoms: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. Although miosis is characteristic of narcotic overdose, mydriasis may occur in terminal narcosis or severe hypoxia. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur. The manifestations of chlorpheniramine overdose may vary from central nervous system depression to coma.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdose or unusual sensitivity to narcotics including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone in this formulation may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

DOSEAGE AND ADMINISTRATION: It is important that TUSSIONEX be measured with an accurate measuring device (see PRECAUTIONS, Information for Patients). A household teaspoon is not an accurate measuring device and could lead to overdose, especially when half a teaspoon is to be measured. It is strongly recommended that an accurate measuring device be used. A pharmacist can provide an appropriate measuring device and can provide instructions for measuring the correct dose.

Shake well before using.

Adults and Children 12 Years and Older: 5 mL (1 teaspoonful) every 12 hours; do not exceed 10 mL (2 teaspoonfuls) in 24 hours.

Children 6-11 Years of Age: 2.5 mL (1/2 teaspoonful) every 12 hours; do not exceed 5 mL (1 teaspoonful) in 24 hours. This medicine is contraindicated in children under 6 years of age (see CONTRAINDICATIONS).

HOW SUPPLIED: TUSSIONEX Pennkinetic (hydrocodone polistirex and chlorpheniramine polistirex) Extended-Release Suspension is a gold-colored suspension.

NDC 52014-548-67 473 mL bottle

For Medical Information: Contact: Medical Affairs Department / Phone: (866) 823-3068 / Fax: (770) 875-8059

Storage: Shake well. Dispense in a well-closed container.

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

TUSSIONEX Pennkinetic Extended-Release Suspension

Manufactured for:

UCB, Inc.

Savannah, GA 30080

UCB

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A Colonoscopy Screen Every 5 Years May Be Safe

For patients at average risk for colorectal cancer whose initial screening colonoscopy reveals no abnormalities, an interval of 5 years or longer before the next exam appears to be safe.

The 5-year risk of colorectal cancer in such patients is extremely low, and the risk of advanced neoplasms also is low—findings that “provide support for rescreening after an interval of 5 years or longer,” said Dr. Thomas F. Imperiale of the Indiana University, Indianapolis, and his associates.

The investigators determined the incidences of any neoplasia and of advanced neoplasia at 5-year rescreening colonoscopy in a population of 1,256 middle-age people at average risk for colorectal cancer. The study subjects had undergone initial screening colonoscopy with 36 gastroenterologists at seven clinical centers in Indiana between 1995 and 2000. A total of 1,057 subjects had no polyps, and 199 had only hyperplastic polyps at that time.

Five years later, they underwent follow-up colonoscopy at a mean age of 57 years. No cancers were discovered.

However, 201 subjects (16%) had neoplastic polyps at rescreening. Sixteen subjects (1.3%) had advanced neoplasms at rescreening. These results are similar to those of previous studies of interval rescreening among people with normal findings on baseline colonoscopy (N. Engl. J. Med. 2008;359:1218-24).

In an editorial comment, Dr. Robert H. Fletcher, professor emeritus at Harvard Medical School, Boston, said that even though intervals of 5-10 years between screenings have been recommended, “in clinical practice, intervals between colonoscopic examinations have apparently not reflected the evidence.

“In a survey, endoscopists in the United States said they performed follow-up colonoscopies at substantially shorter intervals than those recommended by expert groups,” Dr. Fletcher said (N. Engl. J. Med. 2008;359:1285-7).

The study was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases, and no potential conflict of interest was noted. Dr. Fletcher reports serving as a paid consultant for Exact Sciences.

—Mary Ann Moon