Prescribing Information

NEXDOL-8®

Acetaminophen (300 mg), Caffeine Citrate (30 mg), Codeine Phosphate (8 mg) Tablets

NEXDOL-15®

Acetaminophen (300 mg), Caffeine Citrate (30 mg), Codeine Phosphate (15 mg) Tablets

NEXDOL-30®

Acetaminophen (300 mg), Caffeine Citrate (30 mg), Codeine Phosphate (30 mg) Tablets

ANALGESIC - ANTIPYRETIC

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NEXDOL-30

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ANALGESIC - ANTIPYRETIC

INDICATIONS

For the relief of mild to moderate pain and the reduction of fever in adults 18 years and older.

CLINICAL USES

EXDOL is valuable as a non-salicylate analgesic for the relief of pain in a wide variety of arthritic and rheumatic conditions involving musculoskeletal pain as well as in myalgia, neuralgia, headache, toothache and dysmenorrhea; as an antipyretic for symptomatic reduction of fever.

EXDOL is particularly useful for patients who must avoid the gastric irritation caused by acetylsalicylic acid (such as patients with peptic ulcer, gastritis, hiatus hernia, reflux esophagitis and patients on steroid therapy); for patients allergic to acetylsalicylic acid; for patients with bleeding disorders or on anticoagulant therapy.

Pediatrics
Regardless of clinical setting, the use of codeine, including EXDOL, is not recommended in patients below the age of 18 years due to increased safety concerns.

CONTRAINDICATIONS

Sensitivity to any of the components.

Repeated administration of large doses to patients with anemia or with renal disease or with important impairment of hepatic function should be avoided.

Acetaminophen may be contraindicated in patient known glucose-6-phosphate dehydrogenase deficiency.

EXDOL should not be given to children less than 18 years old.

PRECAUTIONS

Acetaminophen
Regular use of acetaminophen has been shown to produce a slight increase in prothrombin time in patients receiving oral anticoagulants but the clinical significance of this effect is not clear.

Renal damage has not been reported following the use of acetaminophen in therapeutic doses, but the chemical relationship of this drug to phenacetin cautions against its use in large amounts over protracted periods of time.

Acetaminophen poisoning can result in severe hepatic damage. Phenobarbital increases the activity of hepatic microsomal enzymes which produce hydroxylated metabolites of acetaminophen responsible for its hepatotoxicity. Thus, concomitant ingestion of phenobarbital may increase the likelihood of liver necrosis in acetaminophen overdose.

Codeine
Care should be observed in the use of codeine although tolerance and addiction to its use are rare.

Codeine should be given with caution to patients with severe respiratory depression. The depressant effect of codeine may be enhanced by the concurrent administration of sedatives and tranquilizers.

Ultra-Rapid Melabolizers of Codeine
Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion or shallow breathing.

Lactation
Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. Despite the common use of codeine products to manage postpartum pain, reports of adverse

events in infants are rare. However, some women are ultra-rapid metabolizers of codeine (see **PRECAUTIONS, Ultra-Rapid Metabolizers of Codeine**). These women achieve higher than expected serum levels of codeine's active metabolite, morphine, leading to higher than expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their- breastfed infants. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants.

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of codeine during breastfeeding.

Respiratory
Codeine, including EXDOL, is not recommended for use in any patient whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, lung infections, multiple trauma or extensive surgical procedures.

Hypersensitivity Reactions
Serious skin reactions
Rarely, acetaminophen can cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens – Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. It is important to recognize and react quickly to the initial symptoms of these reactions which may occur without warning but may be manifested by any serious skin reactions. Patients should be informed about the signs of serious reactions, and use of the drug should be discontinued at their first appearance.

Hepatic
Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of sever hepatotoxicity and death. The maximum daily dose of acetaminophen includes all routes of administration (intravenous, oral and rectal) and all products containing acetaminophen (oral solutions/drops, syrup, pills, capsules, suppositories, etc.). Do not exceed the maximum recommended daily dose of acetaminophen (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Acetaminophen
In recommended therapeutic doses, acetaminophen is usually well tolerated.

The incidence of gastrointestinal upset is less than after salicylate administration.

Skin rash occurs occasionally. The rash is usually erythematous or urticarial.

Codeine
Average or large doses of codeine may cause various gastrointestinal symptoms such as nausea, vomiting and constipation.

Caffeine
Caffeine may cause nausea, nervousness, insomnia, headache, vomiting, palpitation, vertigo, muscle tremor, sensory disturbances, excessive diuresis in sensitive patients. Large doses may cause gastric ulceration.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

OVERDOSAGE

The toxic dose is estimated at 150 mg/kg or greater. In adults, hepatotoxicity may occur after ingestion of a single dose of 10 g (30 or more 325 mg tablets) of acetaminophen; a dose of 25 g or more is potentially fatal. In adults, non-fatal overdoses ranging from 12.5 to 31.5 g have been reported. A child of 13 is reported to have died after ingesting 15 g.

If the history indicates ingestion of a quantity possible in excess of 7.5 g or if information on ingestion is unreliable, treatment should be instituted until the result of the initial plasma assay of acetaminophen is available.

For management of a suspected drug overdose, contact your regional Poison Control Center immediately.

SYMPTOMS

Symptoms during the first 2 days of acute poisoning by acetaminophen do not reflect the potential seriousness of the intoxication.

The first 12-24 hours after ingestion - The patient may experience nausea, vomiting, diaphoresis, or lethargy; some patients with lower blood levels may be completely symptom-free. It is only during this stage that aggressive therapeutic intervention may prevent liver damage and even death.

The next 24-48 hours - The patient becomes - or remains - asymptomatic. At this time, however, liver injury may become manifest initially by elevation of serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration, and prolongation of prothrombin time, which ultimately peak at day 3 or 4. Unless there are problems associated with other medications taken along with the acetaminophen, glucose, electrolyte, and creatinine levels are unchanged.

Day 3 to 5 postingestion - Liver abnormalities become symptomatic. Jaundice, hypoglycaemia, prolongation of prothrombin time, seizures, and coma may culminate in hepatic failure. Secondary renal failure may occur. Liver biopsy reveals centrilobular necrosis with sparing of the periportal area. In nonfatal cases, the hepatic lesions are reversible over a period of weeks or months.

DETERMINATION OF ACETAMINOPHEN CONCENTRATION IN PLASMA

Plasma assays should be taken at least four hours, and at twelve hours, after overdosage. A single determination is a less reliable predictor of hepatic injury. When accurate readings are available, plasma concentrations of 200 μg/mL at 4 hours after ingestion or above 50 μg/mL at 12 hours after ingestion forecast severe liver damage. However, only minimal liver damage has developed when the serum concentrations were below 150 μg/mL at 4 hours or less than 37 μg/mL at 12 hours after ingestion of the drug.

Acetaminophen can be measured in the plasma by methods described by the following authors:

Thomas, B.H., Caldwell, B.B., **J. Pharm. Pharmac., 24:** 243, 1972
Prescott, L.F., **J. Pharm. Pharmac., 23,** 111-115, 1971
Glynn, John P., Kendall, Stephen E., **Lancet**, 1147-1148, May 17, 1975(colorimetric method).

TREATMENT

Although acetaminophen is rapidly absorbed, induction of vomiting or gastric lavage may help reduce drug absorption, if done within a few hours of ingestion. Do not use charcoal lavage because of its interference with acetylcysteine absorption.

Acetylcysteine (Mucomyst®) appears to be an appropriate antidote to counteract acetaminophen's hepatotoxicity. Start acetylcysteine therapy as soon as possible within the first 12 hours after drug ingestion.

For treatment of acetaminophen overdose, most clinicians give 20% acetylcysteine solution orally diluted 1:3 in cola drinks or grapefruit juice. For patients who still cannot tolerate the taste, the drug can be administered by gastric tube. A loading dose of 140 mg/kg has been given, followed by 70 mg/kg every four hours for 17 additional doses, since two to three days are required for acetaminophen blood levels to return to normal. If vomiting occurs within one hour after acetylcysteine, the dose is repeated.

Codeine and related narcotics analgesics depress respiration by an action on the brain stem respiratory centre.

General supportive measures for depressed respiration, e.g. oxygen and artificial respiration.

If signs of codeine overdosage are present, use naloxone or levallorphan as antidotes.

In all cases of suspected overdose immediately contact a Poison Control Centre.

PHARMACOLOGY

Acetaminophen is the major metabolite of phenacetin and acetanilid. Animal and clinical studies have shown acetaminophen to have antipyretic and analgesic effects similar to those of acetylsalicylic acid. Acetaminophen lacks anti-inflammatory effects.

Unlike the salicylates, acetaminophen does not interfere with tubular secretion of uric acid, nor does it affect acid-base balance if taken in therapeutic doses. Also, it does not antagonize the effects of uricosuric agents. Acetaminophen does not interfere with hemostasis and, in particular, does not inhibit platelet aggregation.

Acetaminophen is rapidly and practically completely absorbed from the gastrointestinal tract and is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; 20 to 50% may be bound at the concentrations encountered during acute intoxication.

Plasma concentration reaches a peak in 1/2 to 1 hour; the plasma half-life is 1 to 3 hours. It has been reported that approximately 85% of a 1.0 g dose was recovered from the urine in 24 hours.

About 3% of acetaminophen is excreted unchanged in the urine, and about 80% is excreted in the urine after conjugation in the liver, predominantly with glucuronic acid and to a small extent with sulphuric acid. The glucuronide accumulates in plasma before excretion. A conjugate with cysteine and metabolites produced by hydroxylation and deacetylation have also been detected. The hydroxylated metabolites are responsible for methemoglobin formation and hepatotoxicity.

DOSAGE AND ADMINISTRATION

Usual dose (adults 18 years and older): Take 1 tablet every 4-6 hours. If pain or fever does not respond to 1 tablet, take 2 tablets at next dose, up to a daily maximum of 12 tablets, or as directed by a physician or dentist.

EXDOL should not be used in children less than 18 years old.

Codeine, including EXDOL, should be prescribed at the lowest effective dose for the shortest period of time. Dosing should be as needed every 4 to 6 hours and not on scheduled intervals.

DOSAGE FORMS, COMPOSITION AND PACKAGING

EXDOL-8: Each tablet contains: acetaminophen 300 mg, caffeine citrate 30 mg, codeine phosphate 8 mg and the following non-medicinal ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, starch, stearic acid and talc.

Available in bottles of 30 and 100 tablets.

EXDOL-15: Each tablet contains: acetaminophen 300 mg, caffeine citrate 30 mg, codeine phosphate 15 mg and the following non-medicinal ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, starch, stearic acid and talc.

Available in bottles of 100 and 500 tablets.

EXDOL-30: Each tablet contains: acetaminophen 300 mg, caffeine citrate 30 mg, codeine phosphate 30 mg and the following non-medicinal ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, starch, stearic acid and talc.

Available in bottles of 50 and 500 tablets.

BIBLIOGRAPHY

1. Clark, R., Thompson, R.P.H., Boriakchanyzvat, V.; Widdop, B.; Davidson, A.R.; Goulding, R.; and Williams, R.: "Hepatic damage and death from overdose of paracetamol", Lancet, 1, 66-69, 1973.

2. Farid, N.R., et all: "Haemodialysis in paracetamol self-poisoning", Lancet,. 396-398, August 26, 1972.

3. Goodman, L.S. and Gilman, A.: "The Pharm. Basis of Therapeutics", Fifth edition, Macmillan, 353-347, 1975.

4. Mielke, C.H., Jr et all, J.A.M.A., 6:235, Feb. 9, 1976.

5. MacLean, D. et all: "Treatment of acute paracetamol poisoning", Lancet: 849-852, Oct. 19, 1968.

6. Prescott, L.R.; Swainson, C.P.; Forrest, A.R.W.; Newton,R.W.; Wright, N.; Matthew, H.: "Successful treatment of severe paracetamol overdosage with cysteamine", Lancet, 1, 588, 1974.

7. Prescott, L.R.; Wright, N.; Roscoe, P.; Brown, S.S.: "Plasma-paracetamol half-life and hepatic necrosis in patients with paracetamol overdosage", Lancet, 1519-522, 1971.

8. Proudfoot, A.T.; et Wright, N.: "Acute paracetamol poisoning", Br. Med. J., 3:557-558, 1970.

9. Thompson, J.S.; et Prescott, L.R.: "Liver damage and impaired glucose tolerance after paracetamol overdosage", Br. Med. J., 506, August 27, 1966.

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