Attachment A

TYLENOL® WITH CODEINE TABLETS

LABELING

TYLENOL® with Codeine

tablets C III

(acetaminophen and codeine phosphate tablets)

elixir C V

(acetaminophen and codeine phosphate elixir)

Analgesic

For Oral Use

DESCRIPTION

Each tablet contains:

No. 1 Codeine Phosphate*	7.5 mg
Acetaminophen	300 mg
No. 2 Codeine Phosphate*	15 mg
Acetaminophen	300 mg
No. 3 Codeine Phosphate*	30 mg
Acetaminophen	300 mg
No. 4 Codeine Phosphate*	60 mg
Acetaminophen	300 mg

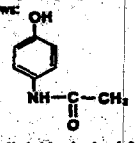
Each 5 mL of elixir contains:

Codeine Phosphate*	12 mg
Acetaminophen	120 mg
Alcohol 7%	

**Warning* — May be habit forming.

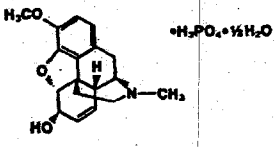
Inactive ingredients: tablets—powdered cellulose, magnesium stearate, sodium metabisulfite†, pregelatinized starch, starch (corn); elixir — alcohol, citric acid, propylene glycol, sodium benzoate, saccharin sodium, sucrose, natural and artificial flavors, FD&C Yellow No. 6.

Acetaminophen, 4'-hydroxyacetanilide, is a nonopiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. Its structure is as follows:



$C_8H_9NO_2$ M.W. 151.16

Codeine is an alkaloid, obtained from opium or prepared from morphine by methylation. Codeine phosphate occurs as fine, white, needle-shaped crystals, or white, crystalline powder. It is affected by light. Its chemical name is: 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate. Its structure is as follows:



$C_{18}H_{21}NO_3 . H_3PO_4 . \frac{1}{2}H_2O$
M.W. 406.37

†See WARNINGS

CLINICAL PHARMACOLOGY

TYLENOL with Codeine (acetaminophen and codeine phosphate tablets and elixir) combine the analgesic effects of a centrally acting analgesic, codeine, with a peripherally acting analgesic, acetaminophen. Both ingredients are well absorbed orally. The plasma elimination half-life ranges from 1 to 4 hours for acetaminophen, and from 2.5 to 3 hours for codeine.

Codeine retains at least one-half of its analgesic activity when administered orally. A reduced first-pass metabolism of codeine by the liver accounts for the greater oral efficacy of codeine when compared to most other morphine-like narcotics. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine. Approximately 10 percent of the administered codeine is demethylated to morphine, which may account for its analgesic activity.

Acetaminophen is distributed throughout most fluids of the body, and 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.

INDICATIONS AND USAGE

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) are indicated for the relief of mild to moderately severe pain.

TYLENOL with Codeine elixir (acetaminophen and codeine phosphate elixir) is indicated for the relief of mild to moderate pain.

CONTRAINDICATIONS

TYLENOL with Codeine tablets or elixir (acetaminophen and codeine phosphate tablets and elixir) should not be administered to patients who have previously exhibited hypersensitivity to any component.

WARNINGS

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

General

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 this product or other narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Special Risk Patients: This drug should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Information for Patients

Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

The patient should understand the single-dose and 24 hour dose limits, and the time interval between doses.

Drug Interactions

Patients receiving other narcotic analgesics, 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.

The concurrent use of anticholinergics with codeine may produce paralytic ileus.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed with acetaminophen or codeine to determine carcinogenic potential or effects on fertility.

Acetaminophen and codeine have been found to have no mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Bauc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Codeine: A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

There are no studies in humans, and the significance of these findings to humans, if any, is not known.

TYLENOL with Codeine (acetaminophen and codeine phosphate tablets and elixir) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:

Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. These signs usually appear during the first few days of life.

Labor and Delivery

Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSAGE). The effect of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

Some studies, but not others, have reported detectable amounts of codeine in breast milk. The levels are probably not clinically significant after usual therapeutic dosage. The possibility of clinically important amounts being excreted in breast milk in individuals abusing codeine should be considered.

Pediatric Use

Safe dosage of TYLENOL with Codeine elixir (acetaminophen and codeine phosphate elixir) has not been established in children below the age of three years.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, shortness of breath, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include allergic reactions, euphoria, dysphoria, constipation, abdominal pain and pruritus.

At higher doses, codeine has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) are a Schedule III controlled substance.

TYLENOL with Codeine elixir (acetaminophen and codeine phosphate elixir) is a Schedule V controlled substance.

Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications.

OVERDOSAGE

Acetaminophen

Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

Codeine

Signs and Symptoms: Serious overdose with codeine 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. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

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 is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including codeine. Therefore, an appropriate dose of naloxone hydrochloride (see package insert) should be administered, preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation. Since the duration of action of codeine 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.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient.

It should be kept in mind, however, that tolerance to codeine can develop with continued use and that the incidence of untoward effects is dose related. Adult doses of codeine higher than 60 mg fail to give commensurate relief of pain but merely prolong analgesia and are associated with an appreciably increased incidence of undesirable side effects. Equivalently high doses in children would have similar effects.

The usual adult dosage for tablets is:

	Single Doses (Range)	Maximum 24 Hour Dose
Codeine Phosphate	*15mg - 60mg*	*360mg*
Acetaminophen	300mg - 1000mg	4000mg

Doses may be repeated up to every 4 hours.

The prescriber must determine the number of tablets per dose, and the maximum number of tablets per 24 hours, based upon the above dosage guidance. This information should be conveyed in the prescription.

For children, the dose of codeine phosphate is 0.5 mg/kg.

TYLENOL with Codeine elixir (acetaminophen and codeine phosphate elixir) contains 120 mg of acetaminophen and 12 mg of codeine phosphate/5 mL and is given orally.

The usual doses are:

Children (7 to 12 years): 10 mL (2 teaspoonfuls) 3 or 4 times daily.
(3 to 6 years): 5 mL (1 teaspoonful) 3 or 4 times daily.
(under 3 years): safe dosage has not been established.

Adults: 15 mL (1 tablespoonful) every 4 hours as needed.

HOW SUPPLIED

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets): (round, white, imprinted "McNEIL", "TYLENOL CODEINE" and either "1", "2", "3", "4"): No. 1 - NDC 0045-0510, bottles of 100; No.2 - NDC 0045-0511, bottles of 100 and 500; No. 3 - NDC 0045-0513, bottles of 20, 30, 50, 100, 500, and 1000; and No. 4 - NDC 0045-0515, bottles of 100 and 500. No. 2, No. 3, and No. 4 also available in unit doses (20 × 25).

TYLENOL with Codeine elixir (acetaminophen and codeine phosphate elixir) contains 120 mg acetaminophen and 12 mg codeine phosphate/5 mL (colored amber, cherry flavored) — NDC 0045-0508, bottles of 1 pint, unit dose cup (10 x 5 mL) and unit dose cup (10 x 15 mL).

Dispense in tight, light-resistant container as defined in the official compendium.

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