

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

EXTRA STRENGTH TYLENOL® NIGHTTIME

Acetaminophen / Diphenhydramine Hydrochloride Caplets
Caplets, 500 mg Acetaminophen / 25 mg Diphenhydramine Hydrochloride, Oral
Analgesic/Sleep Aid

McNeil Consumer Healthcare
Division of Johnson & Johnson Inc.
88 McNabb Street
Markham, Ontario
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RECENT MAJOR LABEL CHANGES

Section 7: Warnings and Precautions, Sensitivity/Resistance	[05/2024]
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

EXTRA STRENGTH TYLENOL® NIGHTTIME (Acetaminophen / Diphenhydramine Hydrochloride Caplets) is indicated for:

- Quick, effective relief of nighttime mild to moderate pain and accompanying sleeplessness associated with back and body pain, headaches, muscle aches and pains, arthritis pain, menstrual pain, dental pain, and aches and pains due to colds and the flu. It also improves the duration of sleep in these circumstances.

1.1 Pediatrics

Pediatrics (<16 years of age):

Safety and effectiveness in children have not been established. EXTRA STRENGTH TYLENOL® NIGHTTIME should not be administered to children under 16 years of age.

1.2 Geriatrics

Evidence from clinical studies suggests that acetaminophen is safe for use in elderly patients. Due to the diphenhydramine hydrochloride component, EXTRA STRENGTH TYLENOL® NIGHTTIME should not be used by elderly patients who experience confusion at night time as it may cause dizziness, sedation and hypotension.

2 CONTRAINDICATIONS

EXTRA STRENGTH TYLENOL® NIGHTTIME is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Causes sedation or sleepiness. Not for daytime use.
- Do not take more than the maximum daily dose. Overdose may result in severe or possibly fatal liver damage.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Evidence from clinical studies suggests that acetaminophen is safe for use in elderly patients.

Because of the diphenhydramine hydrochloride component, EXTRA STRENGTH TYLENOL® NIGHTTIME should not be used by elderly patients who experience confusion at night time as this drug may produce excitation rather than sedation in the elderly.

4.2 Recommended Dose and Dosage Adjustment

Adult use only (16 years and older):

EXTRA STRENGTH TYLENOL® NIGHTTIME is to be taken as a single dose of 2 caplets at bedtime, or as directed by a physician. Do not exceed 2 caplets in 24 hours. Do not take for more than 5 consecutive nights unless directed by a physician.

Health Canada has not authorized an indication for pediatric use. See 1.1 Pediatrics above.

4.5 Missed Dose

Take once at night before bedtime. Do not take twice the recommended dose after a missed dose.

5 OVERDOSAGE

No adverse events associated with overdose have been identified for the combination of diphenhydramine and acetaminophen from the review of post-marketing data and the literature. The information presented below describes overdose with the single active ingredients, diphenhydramine and acetaminophen.

Diphenhydramine

Mild to Moderate Symptoms: Somnolence, anticholinergic syndrome (mydriasis, flushing, fever, dry mouth, urinary retention, decreased bowel sounds), tachycardia, (Flomenbaum 2006) mild hypertension, nausea and vomiting are common after overdose. Agitation, confusion and hallucinations may develop with moderate poisoning (Klasco 2010).

Severe Symptoms: Effects may include delirium, psychosis, seizures, coma, (Dart 2004) hypotension, QRS widening, and ventricular dysrhythmias, including torsades de pointe, but are generally only reported in adults after large ingestions. Rhabdomyolysis and renal failure may rarely develop in patients with prolonged agitation, coma or seizures (Klasco 2010). Death may occur as a result of respiratory failure or circulatory collapse (Dart 2004).

Acetaminophen

Hepatobiliary Disorders In adults and adolescents (≥ 12 years of age), hepatic toxicity may occur following ingestion of greater than 7.5 to 10 grams over a period of 8 hours or less. Fatalities are infrequent (less than 3-4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children (<12 years of age), an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity. Early symptoms following a potentially hepatotoxic overdose may include: anorexia, nausea, vomiting, diaphoresis, pallor and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion (Temple 2005). Serious toxicity or fatalities have been extremely infrequent following an acute acetaminophen

overdose in young children, possibly because of differences in the way they metabolize acetaminophen (Temple 2005).

The following are clinical events associated with acetaminophen overdose that if seen with overdose are considered expected, including fatal events due to fulminant hepatic failure or its sequelae.

Table 1: Adverse Drug Reactions Identified with Overdose of Acetaminophen

<p><i>Metabolism and Nutrition Disorders:</i></p> <p><i>Decreased appetite</i></p> <p><i>Gastrointestinal Disorders:</i></p> <p><i>Vomiting, Nausea, Abdominal discomfort</i></p> <p><i>Hepatobiliary Disorders:</i></p> <p><i>Hepatic necrosis, Acute hepatic failure, Jaundice, Hepatomegaly, Liver tenderness</i></p> <p><i>General Disorders and Administration Site Conditions:</i></p> <p><i>Pallor, Hyperhidrosis, Malaise</i></p> <p><i>Investigations:</i></p> <p><i>Blood bilirubin increased, Hepatic enzymes increased, international normalized ratio increased, Prothrombin time prolonged, Blood phosphate increased, Blood lactate increased</i></p>

The following clinical events are sequelae to acute hepatic failure and may be fatal. If these events occur in the setting of acute hepatic failure (Feldman 2006, Flomenbaum 2006) associated with acetaminophen overdose (adults and adolescents: > 12 years of age:> 7.5 gm within 8 hours; children < 12 years of age: >150 mg/kg within 8 hours), they are considered expected.

Table 2: Expected Sequelae to Acute Hepatic Failure Associated with Acetaminophen Overdose

<p>Infections and Infestations: <i>Sepsis, Fungal infection, Bacterial infection</i></p> <p>Blood and Lymphatic System Disorders: <i>Disseminated intravascular coagulation, Coagulopathy, Thrombocytopenia</i></p> <p>Metabolism: <i>Hypoglycemia, Hypophosphatemia, Metabolic Acidosis, Lactic Acidosis</i></p> <p>Nervous System Disorders: <i>Coma (with massive acetaminophen overdose or multiple drug overdose), Encephalopathy, Brain Oedema</i></p> <p>Cardiac Disorders: <i>Cardiac myopathy</i></p> <p>Vascular Disorders: <i>Hypotension</i></p> <p>Respiratory, Thoracic and Mediastinal Disorders: <i>Respiratory Failure</i></p> <p>Gastrointestinal Disorders: <i>Pancreatitis, Gastrointestinal haemorrhage</i></p> <p>Renal and Urinary Disorders: <i>Acute renal failure</i></p> <p>General Disorders and Administration Site Conditions: <i>Multi-organ failure</i></p>

Blood and Lymphatic Disorders

Haemolytic anaemia (in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency):
Haemolysis has been reported in patients with G6PD deficiency, with use of acetaminophen in overdose (McNeil - Data on File).

Hepatic injury is the principal toxic effect of a substantial acetaminophen overdose. The physician should be mindful that there is no early presentation that is pathognomic for the overdose. A high degree of clinical suspicion must always be maintained.

Untreated acetaminophen overdoses may produce hepatotoxicity. Acetaminophen hepatotoxicity occurs as a threshold effect and is characterized by a lack of toxicity at lower/therapeutic doses. Acetaminophen hepatotoxicity occurs after major depletion of glutathione, an endogenous detoxifying

substance. Once the threshold is exceeded, increasing acetaminophen doses may produce increasing degrees of hepatotoxicity, unless N-acetylcysteine (NAC) is administered.

The clinical course of acetaminophen overdose generally occurs in a three-phase sequential pattern. The first phase begins shortly after ingestion and lasts for 12 to 24 hours. The patient may manifest signs of gastrointestinal irritability, nausea, vomiting, anorexia, diaphoresis, pallor and general malaise. If toxicity continues, there is a latent phase of up to 48 hours. During this second phase, initial symptoms abate and the patient may feel better. However, hepatic enzymes, bilirubin, and prothrombin time or INR values will progressively rise. Right upper quadrant pain may develop as the liver becomes enlarged and tender. Most patients do not progress beyond this phase, especially if given N-acetylcysteine (NAC) treatment early in the course. Signs and symptoms of the third phase depend on the severity of hepatic damage and usually occur from three to five days following overdose ingestion. Symptoms may be limited to anorexia, nausea, general malaise, and abdominal pain in less severe cases or may progress to confusion, stupor and sequelae of hepatic necrosis including jaundice, coagulation defects, hypoglycemia, and encephalopathy, as well as renal failure and cardiomyopathy. Death, if it occurs, is generally the result of complications associated with fulminant hepatic failure. Mortality rates in patients with toxic plasma levels who do not receive antidote therapy range from 3% to 4%.

Due to the wide availability of acetaminophen, it is commonly involved in single and mixed drug overdose situations and the practitioner should screen 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.

Specific Antidote: Any individual presenting with a possible acetaminophen overdose should be treated with N-acetylcysteine (NAC), even if the amount of acetaminophen ingested is unknown or questionable. A blood sample for determination of the plasma acetaminophen concentration should be obtained as early as possible, but no sooner than four hours following ingestion. Do not await the results of assays for plasma acetaminophen levels before initiating treatment NAC. If the acetaminophen plasma level is found to plot above the treatment line on the acetaminophen overdose nomogram, NAC treatment should be continued for a full course of therapy. NAC is used clinically to treat acute acetaminophen overdose, and acts by interacting with the oxidative intermediate, NAPQI. NAC administered by either the i.v. or the oral route is known to be a highly effective antidote for acetaminophen poisoning. It is most effective when administered within 8 hours of a significant overdose but 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. For full prescribing information, consult the product monograph for NAC.

Overdose During Pregnancy: Acetaminophen is one of the most common overdoses in pregnancy. Hepatic toxicity of acetaminophen follows the formation of the highly reactive metabolite N-acetyl-p-benzoquinoneimine produced by acetaminophen metabolism through the cytochrome P450 mixed function oxidase system. Hepatic failure can be prevented by timely administration of NAC either orally for 72 hours, or intravenously (IV) for 20 hours (Prescott 1979, Smilkstein 1988).

Acetaminophen crosses the human placenta so the fetus is theoretically at risk when maternal overdose of acetaminophen occurs (McElhatton 1990). Acetaminophen can be transformed to its toxic metabolite since the oxidative capacity of fetal microsomes is present in the fetus by 14 weeks gestation (Yaffe 1970).

Studies on placental transfer of NAC in rats and sheep yielded conflicting results (Selden 1991). Placental transfer of N-acetylcysteine in humans was demonstrated in 4 women treated with NAC for acetaminophen overdose during labour. NAC blood levels in the fetuses were within the range associated with therapeutic doses of NAC administered to adults with acetaminophen poisoning (Horowitz 1997).

Fetal toxicity and stillbirth after a large (e.g. 30 g) acetaminophen overdose has been reported, but others observed a normal outcome for the offspring after acetaminophen overdose in pregnancy. A large case series investigated the pregnancy outcome in 300 women who had overdosed with acetaminophen. In this group, 118 cases occurred in the first trimester, 103 in the second trimester and 79 in the third trimester. Forty-nine of these mothers were treated with specific antidotes (33 with NAC and 16 with methionine). There were 219 live-born infants, 11 having malformations (including minor); none had been exposed to acetaminophen during the first trimester. Nine women were treated with NAC during the first trimester; there were two elective terminations; two spontaneous abortions, and five healthy babies in this group (McElhatton 1997).

In summary, acetaminophen overdose during pregnancy should be treated according to regular protocols in order to prevent maternal and potentially fetal toxicity. Unless severe maternal toxicity develops, an acetaminophen overdose does not increase the risk for birth defects or adverse pregnancy outcomes.

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 Rumack-Matthew nomogram, timely administration of NAC as required and appropriate follow-up care. Liver function tests should be performed initially and repeated at 24-hour intervals.

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 full recovery.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
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Oral	Caplet/Acetaminophen 500 mg, Diphenhydramine Hydrochloride 25 mg	Carnauba wax, cellulose, corn starch, FD&C blue no.1 aluminum lake, hypromellose, magnesium stearate, polyethylene glycol, polysorbate 80, sodium citrate, sodium starch glycolate, titanium dioxide.
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EXTRA STRENGTH TYLENOL® NIGHTTIME caplets are light blue coloured. Available in child-resistant and tamper-evident bottles of 16 and 40 caplets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Acetaminophen-containing products should be kept out of the reach of children. Packages contain enough medication to seriously harm a child.

Consumers should not exceed 4 g/day of acetaminophen or use two or more acetaminophen-containing products together. This includes combination products that contain acetaminophen. Do not use with other products containing salicylates or any other pain or fever medicine, or with any other product containing diphenhydramine, even one used on skin.

Physicians should be cognizant of and supervise the use of acetaminophen in patients with chronic alcoholism, serious kidney or serious liver disease. Physicians should alert their patients who regularly consume large amounts of alcohol not to exceed the recommended doses of acetaminophen. Alcohol warning: Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive doses of acetaminophen and should ask their doctor whether they should take acetaminophen or other pain relievers or fever reducers.

Extra Strength TYLENOL® Nighttime should not be taken for pain for more than 5 days without consulting a physician. Patients should 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 wheezing, rash, itching or persistent headache occur, as these may be signs of a condition that requires medical attention.

Patients with the following conditions should be advised to consult a physician before using diphenhydramine: a respiratory condition such as emphysema, chronic bronchitis, or acute or chronic bronchial asthma or chronic pulmonary disease; glaucoma; difficulty in urination due to enlargement of the prostate gland.

Diphenhydramine may enhance the sedative effects of central nervous system depressants including alcohol, sedatives, and tranquilizers resulting in marked drowsiness. While taking this product, consumers should be advised to avoid alcoholic beverages and consult their healthcare professional prior to taking with central nervous system depressants.

Gastrointestinal

Extra Strength TYLENOL® Nighttime should be used with caution in patients with stenosing peptic ulcer

or pyloroduodenal obstruction.

Hepatic/Biliary/Pancreatic

Slower metabolism of acetaminophen, increased activity of the cytochrome P450 enzyme system, or depleted glutathione stores are cited as theoretical risk factors for acetaminophen hepatotoxicity in patients with chronic liver disease. However, acetaminophen has been studied in both adults and children with a wide variety of liver diseases including various types of cirrhosis, hepatitis (including hepatitis C), nodular transformation, congenital hepatic fibrosis, and α 1-antitrypsin deficiency. In none of these conditions is there evidence of an increased risk for hepatotoxicity at currently recommended acetaminophen doses but the studies were insufficiently powered to definitely establish the extent of risk.

Forrest et al (1979) compared acetaminophen metabolism following a single 1500 mg dose in normal subjects, patients with mild liver disease, and patients with severe liver disease. There were no significant differences in overall 24-hour urinary excretion of acetaminophen and glucuronide, sulfate, cysteine, and mercapturic acid conjugates, evidence that acetaminophen metabolism was similar to that in normal subjects. However, the elimination half-life was significantly prolonged in patients with severe liver disease.

At the currently recommended doses acetaminophen is a suitable analgesic choice for use in patients with chronic stable liver disease when used under physician supervision.

Acetaminophen may cause hepatotoxicity in situations of intentional overdose (e.g. attempted suicide), unintentional overdose (e.g. overdosing when pain relief is not satisfactory), simultaneous use of multiple acetaminophen-containing preparations, accidental overdose or in very rare cases, after recommended doses, although causality has not been determined. The hepatotoxic reaction can be severe and life-threatening. Early symptoms following a hepatotoxic overdose may include nausea, vomiting, diaphoresis, lethargy, and general malaise. If appropriate treatment is not instituted, these may progress to upper quadrant pain, confusion, stupor, and sequelae of hepatic necrosis, such as jaundice, coagulation defects, hypoglycemia, and encephalopathy. Renal failure and cardiomyopathy may also occur. In the event of known or suspected overdose, treatment with N-acetyl cysteine should be instituted immediately (see **5 OVERDOSAGE**), even when there are no obvious symptoms. Failure to promptly treat acetaminophen hepatotoxicity with N-acetyl cysteine can result in liver failure, leading to liver transplantation and/or death.

Chronic Alcohol Use: Excessive alcohol use may increase risk of liver toxicity from acetaminophen overdose (acute or chronic) (Critchley 1982 and 1983, Kuffner 1997).

Prospective data from Kuffner et al (1997, 2001) demonstrate that chronic alcoholics can take recommended doses of acetaminophen without the added risk of liver injury. In these prospective, placebo-controlled studies; the researchers evaluated an actively drinking group of alcoholics with a high prevalence of malnourishment. The study participants abruptly stopped their daily alcohol intake and took acetaminophen the next day. This should theoretically make them vulnerable to acetaminophen injury because their CYP2E1 would be maximally induced from the alcohol and there would be no alcohol present to compete with acetaminophen for metabolism by CYP2E1. There was no statistically significant difference in mean values for AST, ALT or INR for alcoholics given four grams per

day of acetaminophen compared to placebo. Additionally, the researchers performed an analysis of the malnourished patients that showed there was no increase in AST or ALT levels in these patients. Study limitations include a limited duration of 2 days and exclusion of patients with pre-existing AST or ALT elevations greater than 120 U/L. Study results do not preclude the possibility of an idiosyncratic hepatic reaction.

Ophthalmologic

Due to the anti-cholinergic properties of diphenhydramine, Extra Strength TYLENOL® Nighttime should not be used in patients with a history of increased intraocular pressure (glaucoma).

Renal

Based on available clinical data, acetaminophen can be used in patients with chronic renal disease without dosage adjustment. Martin et al (1991) found that patients with chronic renal failure had higher plasma concentrations of acetaminophen and the inactive glucuronide and sulfate metabolites than healthy subjects during repeated dosing up to ten days.

Several single-dose studies demonstrate accumulation of acetaminophen metabolites in patients with moderate chronic renal failure and in anephric patients for whom hemodialysis appeared to be the major route of elimination (Lowenthal 1976, Chan 1997, Prescott 1989, Øie 1975).

The habitual consumption of acetaminophen should be discouraged. If indicated medically, the long-term use of acetaminophen should be supervised by a physician.

A National Kidney Foundation position paper notes that physicians preferentially recommend acetaminophen to patients with renal failure because of the bleeding complications associated with ASA use in these individuals (Henrich 1996). Acetaminophen was recommended as the non-narcotic analgesic of choice for episodic use in patients with underlying renal disease.

Extra Strength TYLENOL® Nighttime should not be used in patients with bladder neck obstruction.

Respiratory

Extra Strength TYLENOL® Nighttime should not be used in patients with chronic lung disease, unless directed by a physician.

Sensitivity/Resistance

Sensitivity reactions to acetaminophen are rare and may manifest as rash, urticaria, dyspnea, hypotension, laryngeal edema, angioedema, bronchospasm, or anaphylaxis. Cross-reactivity in ASA-sensitive persons has been rarely reported.

Serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens - Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported very rarely in patients receiving acetaminophen. Patients should

be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies of diphenhydramine, acetaminophen or the combination in pregnant women. This product should not be used during pregnancy unless the potential benefit of treatment to the mother outweighs the possible risk to the developing fetus.

Currently there is no evidence to suggest that acetaminophen is teratogenic when used as recommended. However, data for continuous high daily doses are not sufficient, and safety during pregnancy has not yet been established.

Issues of risks in pregnancy are multifactorial. The information provided cannot be substituted for direct patient consultation. Acetaminophen is believed to be non-teratogenic in humans.

However, existing studies have not assessed the effect of very high doses. The Motherrisk Collaborative Perinatal project monitored 50,282 mother-child pairs, of which 226 had first trimester exposure to acetaminophen and 781 had used acetaminophen at any time during their pregnancy. No evidence was found to suggest a relationship between acetaminophen use and major or minor malformations (Briggs 2002). In a surveillance study of Michigan Medicaid recipients conducted between 1985 and 1992 involving 229,101 completed pregnancies, 9,146 newborns had been exposed to acetaminophen during the first trimester (Briggs 2002). This data does not support an association between acetaminophen use and the occurrence of birth defects. Another cohort study, using prescription monitoring, found no excess risk for malformation, and no evidence that acetaminophen influenced fetal growth (Thulstrup 1999). Finally, as part of a larger study, 697 women used acetaminophen with or without codeine in their first trimester. No teratogenic risk was found (Aselton 1985).

A prospective study investigated the outcome of pregnancy in 300 women who had self-administered an overdose of acetaminophen, either alone, or as part of a combined preparation. Exposure to overdose occurred in all trimesters. The majority of the pregnancies had normal outcomes. The malformation rate was within the expected range. There was no obvious relationship between the time of exposure and the time of delivery. The overall conclusion was that acetaminophen overdose is not an indication for termination of pregnancy (McElhatton 1997).

In a long-term developmental follow-up study, acetaminophen did not adversely affect IQ or behavior measures at four years of age (Streissguth 1987). Height, weight and head circumference were also not affected by exposure to acetaminophen in utero.

Unlike ASA, which has been shown to profoundly affect platelet function, there does not seem to be a risk of hemorrhage associated with acetaminophen use at term (Pearson 1978, Rudolph 1981).

A review by Quinlan et al (2003), states that diphenhydramine has been used to control nausea and vomiting during pregnancy. One study found an association between diphenhydramine and cleft lip and palate, but a subsequent study did not support this finding (Quinlan 2003).

7.1.2 Breast-feeding

There are no adequate and well-controlled studies of diphenhydramine, acetaminophen or the combination in breast-feeding women. This product should not be used during breastfeeding unless the potential benefit of treatment to the mother outweighs the possible risk to the nursing infant.

7.1.3 Pediatrics

Safety and effectiveness in children have not been established. EXTRA STRENGTH TYLENOL® NIGHTTIME should not be administered to children under 16 years of age.

7.1.4 Geriatrics

Acetaminophen at currently recommended doses can be used safely by elderly patients. Results of well-designed clinical studies indicate that a dose reduction of acetaminophen, to avoid potential increased risk for toxicity, is not necessary. In a comprehensive metabolic study by Miners et al (1988), the formation and clearance of glucuronide and glutathione conjugates were the same in young and elderly adults, although clearance of the sulphate conjugate and unchanged acetaminophen were reduced. This finding provides prospective scientific data that the amount of acetaminophen metabolized via the oxidative pathway, from which the highly reactive intermediate, NAPQI, is generated, does not increase with age. Recently, Bannwarth et al (2001) evaluated the multiple-dose pharmacokinetics of acetaminophen in elderly patients. After seven days of repeat dosing, acetaminophen did not accumulate in the plasma, and the elimination half-life was the same as that reported for young adults.

Elderly patients who require therapy for longer than 5 days should consult their physician for condition monitoring; however, no reduction in recommended dosage is necessary. The American Geriatrics Society Clinical Practice Guidelines for the Management of Chronic Pain in Older Persons (1998) recommend acetaminophen as the drug of choice for relieving mild to moderate musculoskeletal pain, with the maximum dosage not to exceed 4000 mg daily.

Acetaminophen is safe for use in the elderly population as currently labelled.

Because of the diphenhydramine hydrochloride component, Extra Strength TYLENOL® Nighttime should not be used by elderly patients who experience confusion at night time as it may cause dizziness, sedation and hypotension.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Results of clinical trials conducted with Extra Strength TYLENOL® Nighttime caplets have shown that this combination product presents no additional risk compared to its individual active ingredients.

Adverse Drug Reactions of Acetaminophen

Central Nervous System Effects: Acetaminophen at recommended doses has no obvious effects on central nervous system function. In an overdose situation, central nervous system effects are

uncommon.

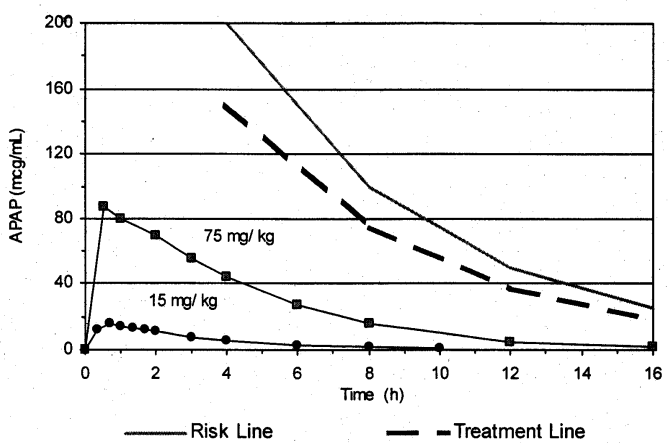
Gastrointestinal Effects: Acetaminophen at recommended doses does not cause gastric irritation, gastric erosions, occult or overt gastrointestinal blood loss or ulcers (Hoftiezer 1982, Johnson and Driscoll 1981). Blot and McLaughlin (2000) conducted an independent analysis of case-control data from a study conducted by the American College of Gastroenterology. The risk of gastrointestinal bleeding increased two to three-fold among recent users of ASA, ibuprofen and other NSAIDs at OTC doses, and the risk was also dose-related. In contrast, the use of acetaminophen was not associated with an increased risk of gastrointestinal bleeding.

Hematologic Effects: Acetaminophen does not have any immediate or delayed effects on small vessel hemostasis, as measured by bleeding time. In normal volunteers receiving a single dose of acetaminophen (975 or 1950 mg) or multiple doses of acetaminophen (1950 mg daily for 6 weeks), no change in bleeding time or platelet aggregation was observed (Mielke 1976). In another study, a single 1000 mg dose of acetaminophen was given to normal volunteers and did not affect bleeding time or platelet aggregation (Seymour 1984). Patients with hemophilia receiving multiple doses of acetaminophen showed no significant changes in bleeding time (Kasper and Rapaport 1972, Mielke 1981).

Hematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported, although these are rare and causality has not been established.

Hepatic Effects: As an illustration of the margin of safety of acetaminophen at supratherapeutic doses, a comparison of serum concentrations of acetaminophen over time for a standard 15 mg/kg dose and for a dose exceeding the standard by a multiple of 5 (75 mg/kg) are shown in Figure 1. The serum concentrations are drawn relative to the risk line for hepatotoxicity and treatment line of the Rumack-Matthew nomogram used to manage acute overdoses. The mean plasma concentrations for this supratherapeutic dose are well below the risk and treatment lines of the nomogram at all times. However, to minimize the risk for adverse effects, the maximum recommended dose should not be exceeded.

Figure 1: Mean Data for a Standard (1 g, 15 mg/kg) and Higher (5.6 g, 75 mg/kg) Dose Relative to Risk and Treatment Lines of the Acetaminophen Nomogram



Acetaminophen in overdose may cause hepatotoxicity. In adults and adolescents, hepatotoxicity may occur following ingestion of greater than 150 mg/kg over a period of 8 hours or less. Fatalities are infrequent (less than 3% to 4% of untreated cases in which blood levels exceed the treatment line) and have rarely been reported with overdoses less than 7.5 g. In children, amounts less than 150 mg/kg are unlikely to produce hepatotoxicity. In both adults and children, toxicity associated with acetaminophen is usually caused by ingestion of quantities of the drug that are significantly above the recommended dosage range. Hepatotoxicity, ranging from transient sharp transaminase elevations to fatal, fulminant hepatic failure, is the most common result of clinically significant overdose (Linden and Rumack 1984).

In a double-blind, placebo-controlled clinical study, healthy adults were given 4, 6 and 8 g/d of acetaminophen over 3 days (Gelotte 2003). Plasma concentrations did not accumulate with repeat doses. Clinically all doses were well tolerated by the subjects and aminotransferase values stayed within normal limits throughout the study. These data provide information related to the margin of safety but are not intended to support dosing beyond the maximum recommended dose of 4 g/day.

A report has suggested that hepatotoxicity following greater than the recommended dose of acetaminophen may be enhanced by both prolonged fasting and/or chronic alcohol abuse (Whitcomb and Block 1994).

Acute Alcohol Use: Acute alcohol ingestion refers to the occasional or intermittent use of alcohol. When taken together, alcohol competes with acetaminophen for CYP2E1. CYP2E1 accepts alcohol more readily than acetaminophen; therefore, less NAPQI is produced (Forrest 1982). In the presence of alcohol, acetaminophen may be diverted to the glucuronidation and sulfation pathways. The overall result is that a smaller percentage of acetaminophen may be expected to be metabolized to the toxic intermediate, NAPQI, than would otherwise be the case (Rumack 2002). NAPQI production is increased above baseline for the period up to 18-24 hours post ethanol clearance from the body. In healthy adults, at normal labeled doses of acetaminophen, the temporary increase in NAPQI production is more than accommodated by normal glutathione stores in the liver.

Hypersensitivity: Sensitivity reactions are rare and may manifest as rash, urticaria, dyspnea, hypotension, laryngeal edema, angioedema, bronchospasm, or anaphylaxis. Cross-reactivity in ASA-sensitive persons has been rarely reported. If sensitivity is suspected, discontinue use of the drug.

Renal Effects: Acute nephrotoxicity has been reported following massive overdose either as a sequela of hepatic failure or, occasionally, in the absence of hepatic failure (Rumack and Matthew 1975). Clinical data have established that acetaminophen in recommended doses is not nephrotoxic.

Some studies suggest an association between the chronic long-term use of acetaminophen and renal effects. Results, however, are conflicting, limited by recall bias and confounded by the inability to determine whether analgesic use preceded or followed the onset of renal disease (Edwards 1971, Gates & Temple 1989, Murray 1983, Nelson 1995, Perneger 1994, Sandler 1989).

Case control studies have suggested a weak association between habitual acetaminophen use and prevalence of chronic renal failure and end stage renal disease (Heinrich 1996). This National Kidney Foundation position paper concludes that acetaminophen has been preferentially recommended by physicians to patients with renal failure and that there is no evidence that occasional use of acetaminophen caused renal injury. In this position paper, acetaminophen was recommended as the non-narcotic analgesic of choice for episodic use in patients with underlying renal disease.

Adverse Drug Reactions of Diphenhydramine Hydrochloride

Drowsiness, dizziness, dryness of mouth, nausea and nervousness may occur with the use of diphenhydramine. Other infrequently reported effects include vertigo, palpitations, blurred vision, headache, restlessness, insomnia and thickening of the bronchial secretions.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of the combination of diphenhydramine and acetaminophen from clinical trial data is based on data from 6 randomized, placebo-controlled single dose clinical trials for the treatment of pain secondary to osteoarthritis with sleeplessness, the management of dental pain with sleeplessness, and insomnia with mild pain (McNeil - Data on File).

Table 3 includes adverse events that occurred where greater than one event was reported, and the incidence was greater than placebo and in 1% of patients or more. A dash represents an incidence of less than 1%.

Table 3: AEs Reported by \geq 1% of Diphenhydramine/Acetaminophen–treated Subjects in 6 Randomized, Placebo-Controlled Trials

System Organ Class Preferred Term	*Diphenhydramine 50 mg 3 times/day (N=936) % (frequency)	Diphenhydramine / Acetaminophen 50 mg/1000 mg Single Dose (N=565) % (frequency)	Placebo (N=370) %
Nervous System Disorders			
<i>Dizziness</i>	2.4 (Common)	1.4 (Common)	-
<i>Somnolence</i>	22.3 (Very Common)	1.9 (Common)	1.9
Gastrointestinal Disorders			
<i>Dry mouth</i>	3.6 (Common)	-	1.1
General Disorders and Administration Site Conditions			
<i>Asthenia</i>	4.4 (Common)	-	-

*ADRs reported by $\geq 2\%$ of single-ingredient diphenhydramine treated subjects in 5 randomized clinical trials

8.5 Post-Market Adverse Reactions

Adverse drug reactions (ADRs) identified during post-marketing experience with diphenhydramine, acetaminophen or the combination are included in Table 4 and Table 5. The frequencies are provided according to the following convention:

Very common $\geq 1/10$

Common $\geq 1/100$ and $< 1/10$

Uncommon $\geq 1/1,000$ and $< 1/100$

Rare $\geq 1/10,000$ and $< 1/1,000$

Very rare $< 1/10,000$

Not known (cannot be estimated from the available data)

In Table 4, ADRs identified are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available or 2) when incidence is unavailable, frequency category is listed as Not known.

In Table 5, the same ADRs are presented with ADR frequency categories estimated from spontaneous reporting rates where the numerator represents total number of reported Company AEs under given PT or medical concept and denominator represents exposure data calculated from sales data.

Table 4: Adverse Drug Reactions Identified During Post-Marketing Experience with Diphenhydramine, Acetaminophen or the Combination by Frequency Category Estimated from Clinical Trials or Epidemiology Studies

SOC	
Frequency Category	Adverse Event Preferred Term
Immune System Disorders	
Not known	<i>Anaphylactic reaction</i>
Not known	<i>Hypersensitivity</i>
Psychiatric Disorders	
Uncommon	<i>Confusional state</i>
Uncommon	<i>Irritability</i>
Uncommon	<i>Nervousness</i>
Not known	<i>Hallucination</i>
Not known	<i>Psychomotor hyperactivity</i>
Nervous System Disorders	
Very common	<i>Sedation</i>
Uncommon	<i>Agitation</i>
Uncommon	<i>Insomnia</i>
Not known	<i>Coordination abnormal</i>
Not known	<i>Convulsion</i>
Not known	<i>Headache</i>
Not known	<i>Paraesthesia</i>
Not known	<i>Tremor</i>
Cardiac Disorders	
Not known	<i>Palpitations</i>
Not known	<i>Tachycardia</i>
Vascular Disorders	
Not known	<i>Hypotension</i>
Eye Disorders	
Not known	<i>Vision blurred</i>
Ear and Labyrinth Disorders	
Uncommon	<i>Tinnitus</i>
Respiratory, Thoracic and Mediastinal Disorders	
Common	<i>Dry throat</i>
Not known	<i>Chest discomfort</i>
Not known	<i>Nasal dryness</i>
Gastrointestinal Disorders	
Not known	<i>Constipation</i>

SOC	
Frequency Category	Adverse Event Preferred Term
Not known	<i>Diarrhoea</i>
Not known	<i>Dyspepsia</i>
Not known	<i>Nausea</i>
Not known	<i>Vomiting</i>
Skin and Subcutaneous Tissue Disorders	
Uncommon	<i>Rash</i>
Not known	<i>Fixed eruption</i>
Not known	<i>Pruritus</i>
Not known	<i>Rash pruritic</i>
Not known	<i>Urticaria</i>
Renal and Urinary Disorders	
Not known	<i>Urinary retention</i>
Investigations	
Not known	<i>Transaminases increased[†]</i>

[†]Low level transaminase elevations may occur in some patients taking labeled doses of acetaminophen; these elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of acetaminophen.

Table 5: Adverse Drug Reactions Identified During Post-Marketing Experience with Diphenhydramine, Acetaminophen by Frequency Category Estimated from Spontaneous Reporting Rates

SOC	
Frequency Category	Adverse Event Preferred Term
Immune System Disorders	
Very rare	<i>Anaphylactic reaction</i>
Very rare	<i>Hypersensitivity</i>
Psychiatric Disorders	
Very rare	<i>Confusional state</i>
Very rare	<i>Hallucination</i>
Very rare	<i>Irritability</i>
Very rare	<i>Nervousness</i>
Very rare	<i>Psychomotor hyperactivity</i>
Nervous System Disorders	
Very rare	<i>Agitation</i>
Very rare	<i>Coordination abnormal</i>
Very rare	<i>Convulsion</i>
Very rare	<i>Headache</i>
Very rare	<i>Insomnia</i>
Very rare	<i>Paraesthesia</i>
Very rare	<i>Sedation</i>
Very rare	<i>Tremor</i>
Cardiac Disorders	
Very rare	<i>Palpitations</i>
Very rare	<i>Tachycardia</i>
Vascular Disorders	
Very rare	<i>Hypotension</i>
Eye Disorders	
Very rare	<i>Vision blurred</i>
Ear and Labyrinth Disorders	
Very rare	<i>Tinnitus</i>
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	<i>Chest discomfort</i>
Very rare	<i>Dry throat</i>
Very rare	<i>Nasal dryness</i>
Gastrointestinal Disorders	
Very rare	<i>Constipation</i>
Very rare	<i>Diarrhoea</i>

SOC	
Frequency Category	Adverse Event Preferred Term
Very rare	<i>Dyspepsia</i>
Very rare	<i>Nausea</i>
Very rare	<i>Vomiting</i>
Skin and Subcutaneous Tissue Disorders	
Very rare	<i>Fixed eruption</i>
Very rare	<i>Pruritus</i>
Very rare	<i>Rash</i>
Very rare	<i>Rash pruritic</i>
Very rare	<i>Urticaria</i>
Renal and Urinary Disorders	
Very rare	<i>Urinary retention</i>
Investigations	
Very rare	<i>Transaminases increased[†]</i>

[†]Low level transaminase elevations may occur in some patients taking labeled doses of acetaminophen; these elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of acetaminophen.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Specific clinical trials evaluating the drug interactions with the Extra Strength TYLENOL[®] Nighttime combination have not been conducted. Drug interactions with the individual active ingredients are well-documented.

9.4 Drug-Drug Interactions

Acetaminophen

Alcohol

Studies evaluating the metabolism of doses up to 20 mg/kg of acetaminophen in chronic alcohol abusers and a study evaluating the effects of 2 days of acetaminophen dosing at 4000 mg/day in chronic alcoholics undergoing detoxification, have yielded inconsistent results with regard to effects on acetaminophen pharmacokinetics and demonstrate no evidence of adverse effect on liver function tests (Critchley 1982, 1983, Kuffner 1997, 2001, Skinner 1990, Villeneuve 1983).

Anticoagulants

Patients who concomitantly medicate with warfarin-type anticoagulants and regular doses of acetaminophen have occasionally been reported to have unforeseen elevations in their international normalized ratio [INR]. Physicians should be cognizant of this potential interaction and monitor the INR in such patients closely while therapy is established. Many factors, including diet, medications and environmental and physical states, may affect how a patient responds to anticoagulant therapy (Physicians' Desk Reference® 1999). There have been several reports that suggest that acetaminophen may produce hypoprothrombinemia (elevated INR or prothrombin time) when administered with coumarin derivatives. In other studies, prothrombin time did not change (Antlitz & Awalt 1969, Kwan 1999, Udall 1970). Reported changes have been generally of limited clinical significance; however, periodic evaluation of prothrombin time should be performed when these agents are administered concurrently.

In the period immediately following discharge from the hospital or whenever other medications are initiated, discontinued, or taken regularly, it is important to monitor patient response to anticoagulation therapy with additional prothrombin time or INR determinations (Physicians' Desk Reference® 1999). Despite the potential for interaction, acetaminophen is the least likely OTC analgesic to interfere with anticoagulant therapy and thereby remains the OTC analgesic of choice for concomitant use.

Anticonvulsants

Some reports have suggested that patients taking long-term anticonvulsants, who overdose on acetaminophen, may be at increased risk of hepatotoxicity because of accelerated metabolism of acetaminophen (Bray 1992, Miners 1984). Available data are conflicting. A 7-year retrospective study of acetaminophen overdose admissions indicates that the overall mortality rate was not significantly different for patients taking concomitant anticonvulsant medications (Makin 1995).

Carbamazepine

At usual oral therapeutic doses of acetaminophen and carbamazepine, no special dosage

adjustment is generally required. Carbamazepine is primarily metabolized by CYP3A4 (Levy 1995), whereas acetaminophen is metabolized primarily via CYP2E1. It is not known whether there is increased risk from an acetaminophen overdose in patients on chronic carbamazepine therapy.

Hydantoins

At usual oral therapeutic doses of acetaminophen and hydantoins, no special dosage adjustment or monitoring is generally required. Pharmacokinetic studies indicate that phenytoin primarily induces the glucuronidation pathway, whereas glutathione-derived metabolites are not increased in patients on chronic phenytoin therapy (Prescott 1981). Additionally, data demonstrate that phenytoin is metabolized primarily by CYP2C9 and CYP2C19 (Levy 1995), whereas acetaminophen is primarily metabolized by CYP2E1 (Slattery 2002). These data indicate that there is no increased risk of acetaminophen hepatotoxicity in patients on chronic hydantoin therapy who use the recommended dose of acetaminophen.

Diflunisal

Professional literature from the manufacturer of diflunisal cautions that concomitant administration of diflunisal with acetaminophen increases plasma acetaminophen concentrations by approximately 50% in normal volunteers. Acetaminophen had no effect on diflunisal plasma levels. The clinical significance of this finding has not been established; however, caution should be exercised with concomitant administration of diflunisal and acetaminophen and patients should be monitored carefully.

Isoniazid

Some reports suggest that patients on chronic isoniazid therapy may be at risk for developing hepatotoxicity from an acetaminophen overdose. Since patients on isoniazid therapy may develop hepatic effects from isoniazid alone, data from individual case reports are unclear as to whether chronic administration of isoniazid may increase the risk of acetaminophen toxicity. Isoniazid is primarily metabolized by CYP2E1 and induces CYP2E1. Studies in healthy subjects demonstrate that isoniazid blocks the formation of the toxic metabolite NAPQI when administered concomitantly with acetaminophen, but increases NAPQI formation when acetaminophen is administered one day after discontinuation of isoniazid. Thus, concomitant use of isoniazid is unlikely to potentiate the risk of acetaminophen-induced hepatotoxicity at recommended doses. The isoniazid induction of CYP2E1 is short-lived, lasting only 12 to 48 hours after the discontinuation of isoniazid; it is during this period the toxicity of an acetaminophen overdose may be potentiated.

Diphenhydramine Hydrochloride

Diphenhydramine inhibits CYP2D6 leading to a clinically significant drug-drug interaction when co-administered with compounds that likewise require metabolism via cytochrome P450, such as with metoprolol, tricyclic antidepressants, antiarrhythmic drugs, antipsychotics and tramadol (Bartra 2006, Sharma 2003). Diphenhydramine may enhance the sedative effects of central nervous system depressants, including alcohol (Cohen 1987, Burns 1980) sedatives and tranquilizers.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Acetaminophen

Acetaminophen (N-acetyl-p-aminophenol, 4-hydroxyacetanilide) is an analgesic and antipyretic drug, with minimal or no anti-inflammatory effects. Although the precise mechanism of action is not totally understood, work by Boutaud et al (2002) suggests acetaminophen is an inhibitor of the peroxidase portion of cyclooxygenase (prostaglandin H synthase inhibitor) and that the concentration of hydroperoxide contributes to the cellular selectivity in its action. Depending on the redox state and substrate concentrations surrounding the enzymes, acetaminophen may or may not have a significant inhibitory effect. This accounts for its selective activity on pain and fever with little anti-inflammatory effect. At therapeutic doses, acetaminophen does not inhibit cyclooxygenase (COX) in peripheral tissues which would explain its weak anti-inflammatory activity (Ouellet 2001).

It is postulated that the analgesic effect is produced by elevation of the pain threshold and the antipyretic effect is produced through action on the hypothalamic heat-regulating centre.

Although the exact site and mechanism of analgesic action is not clearly defined, acetaminophen appears to produce analgesia by elevation of the pain threshold (Flower 1985, Guzman 1964, Lim 1964). The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P (Bjorkman 1994).

Investigations indicate that endogenous pyrogens produced by leukocytes cause an elevation of prostaglandin E (PGE) in the cerebrospinal fluid. Fever results when the elevated PGE acts on the preoptic area of the anterior hypothalamus to decrease heat loss and increase heat gain.

Acetaminophen has been shown to inhibit the action of endogenous pyrogens on the heat-regulating

centers in the brain by blocking the formation and release of prostaglandins in the central nervous system (Ameer 1977, Atkins 1974, Koch-Weser 1976, Milton 1976). Inhibition of arachidonic acid metabolism is not requisite for the antipyretic effect of acetaminophen (Clark 1985). Acetaminophen does not depend upon the activation of the arginine vasopressin V-1 receptor to induce antipyresis as has been noted in rats treated with indomethacin and salicylates (Wilkinson 1990, 1993). This has been demonstrated in animals by observing a decrease in both fever and PGE activity following administration of acetaminophen to unanesthetized cats, and in rabbits and dogs when brain prostaglandin synthetase was inhibited by the administration of acetaminophen (Feldberg 1972, Flower 1972).

In Vitro & Animal Data:

Pharmacology studies have been conducted on the individual active ingredients. Pharmacology studies in rats demonstrated that orally administered acetaminophen produced analgesia comparable to that of phenacetin and elevated pain threshold in rabbits given electric shock. The mechanism of action of acetaminophen is related to its ability to block the biosynthesis of prostaglandins with specific inhibition of prostaglandin synthetase in the central nervous system, explaining its lack of anti-inflammatory activity (Ameer and Greenblatt 1977).

Diphenhydramine Hydrochloride

Diphenhydramine competes with histamine for H1 receptor sites on effector cells in the gastrointestinal tract, blood vessels and respiratory tract. Anticholinergic and sedative effects are also seen (Merck Manuals Online Medical Library).

Diphenhydramine is a first-generation antihistamine and is a H1 receptor antagonist. Antagonism is achieved through blocking the effect of histamine more than blocking its production or release. Diphenhydramine inhibits most responses of smooth muscle to histamine and the vasoconstrictor effects of histamine. The antagonism may also produce anticholinergic effects, antiemetic effects, and significant sedative side effects.

In Vitro & Animal Data:

Diphenhydramine showed histamine-H1-antagonist activity in several animal models, including the rat. In addition to antihistaminic activity, diphenhydramine also demonstrated effective antimuscarinic and antiserotonin activities in studies conducted in adult Wistar rats (Niemegeers 1982).

10.2 Pharmacodynamics

Acetaminophen

Acetaminophen is a centrally acting, non-opiate, non-salicylate analgesic. Acetaminophen is a clinically proven analgesic/antipyretic, and it is thought to produce analgesia by elevation of the pain threshold (Flower 1985, Guzman 1964, Lim 1964) and antipyresis through action on the hypothalamic heat-regulating center (Ameer 1977, Atkins 1974, Koch-Weser 1976, Milton 1976).

The optimal effective analgesic dose of acetaminophen was demonstrated in dental pain studies and is 1000 mg every four to six hours, up to 4000 mg daily. At least 500 published and unpublished controlled clinical trials in adults and children have evaluated acetaminophen for the relief of pain or fever. These

studies include single and multiple dose treatments. Most studies were less than 14 days in duration, although the longest study duration was two years. No significant safety issues were reported in any of these studies.

Moreover, at recommended doses, acetaminophen has not been shown to increase the risk of developing renal diseases or upper gastrointestinal ulceration/bleeding (Edwards 1971, Hofteizer 1982, Johnson and Driscoll 1981, Langman 1994, Peura 1997, Prescott 1990, Rexrode 2001, Singh 2000). This observation is consistent with its minimal inhibitory effect on peripheral prostaglandin synthesis and on gastric prostaglandin synthesis (Cryer 2002, Jackson 1984).

Acetaminophen is considered equipotent to ASA and ibuprofen, within the recommended OTC dosing ranges, in its analgesic and antipyretic effects. Acetaminophen at recommended doses does not cause the type of gastrointestinal complications associated with NSAID-containing products, such as gastric irritation, gastric erosions, occult or overt gastrointestinal blood loss, or ulcers. Unlike these drugs, however, acetaminophen has no anti-inflammatory effect at clinically relevant doses in humans.

Diphenhydramine Hydrochloride

Diphenhydramine is an ethanolamine and a first-generation H1 antagonist. It is a reversible, competitive inhibitor of histamine and binds to the H1 receptor. H1 antagonists, especially ethanolamines, have significant antihistaminic activity and antimuscarinic activity and concurrent sedative properties (Hoffman 2001).

The sedative mechanism for diphenhydramine is thought to result from antagonism of central histamine and cholinergic receptors by intact diphenhydramine. The time course for sedation following a 50-mg oral dose was associated with higher plasma concentrations, and was significantly different from placebo during the first three hours following administration (Carruthers 2978). The pharmacodynamics of sedation was correlated with peak concentrations of drug occurring during absorption and the alpha distribution phase (Simons 1990, McNeil - Data on File).

10.3 Pharmacokinetics

Acetaminophen

Absorption

Oral acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract primarily in the small intestine. This absorption process occurs by passive transport. Peak plasma concentrations occur within 0.4 to 1 hour depending on the product formulation. The rate of oral absorption depends mainly upon the rate of gastric emptying (Forrest 1982, Raffa 2014, Marzuillo 2014, Djerf 2015, Dollery 1999).

The relative bioavailability ranges from 85% to 99% (McGilveray 1971, Liu 2015). Peak plasma concentrations are usually attained about 30–60 minutes after oral dosing (Sweetman 2011, Grosser 2011).

For individual adults, maximum plasma concentrations occur within 1 hour following ingestion, and range from 14.8 to 17.6 µg/mL for a single 1000 mg dose (McNeil - Data on File).

Maximum plasma concentrations at steady state after 1000 mg doses every 6 hours range from 17.6 to 18.2 µg/mL (McNeil Data on File). Pooled pharmacokinetic data from five company-sponsored studies for 59 febrile children, ages 6 months to 11 years, found that a mean maximum concentration of 12.08 ± 3.92 µg/mL was attained at 51 ± 39 min (median, 35 min) following a 12.5 mg/kg dose (Pigeon 1978, Byerly 1986, McNeil - Data on File, Gelotte 1994).

Following a single-dose of two gelatin-coated caplets of 1000 mg acetaminophen and 50 mg diphenhydramine HCl, the mean plasma concentrations of 14.2 µg/mL and median TMAX of 1 hour for acetaminophen are within the reported ranges for single-ingredient products (McNeil - Data on File).

Although maximum concentrations of acetaminophen are delayed when administered with food, the extent of absorption is not affected (Forrest 1982, Raffa 2014, Moore 2015).

Acetaminophen can be taken independently of mealtimes (Forrest 1982).

Distribution

Acetaminophen is uniformly distributed throughout most body fluids, but not in fatty tissue. As a result, the volume of distribution in adults ranges between 0.8 and 1.0 L/kg (Forrest et al.1982, Ameer 1983). Since acetaminophen has low protein binding in plasma of only 10% to 25%, it does not compete with drugs that are highly protein bound (Levy 1981, Milligan 1994).

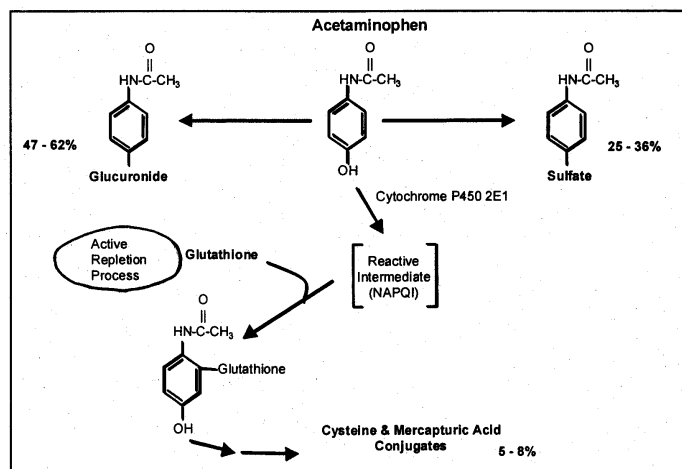
Metabolism

Acetaminophen is primarily metabolized by the liver via three principal separate pathways: conjugation with glucuronide, conjugation with sulfate and oxidation via the cytochrome P450 mixed function oxidase system (Slattery 2002).

Both the glucuronic and oxidative pathways adhere to a first-order rate process, which means the concentration of acetaminophen metabolized increases as the concentration in the liver increases. The sulfate pathway adheres to the Michaelis-Menten kinetics, which means the concentration of acetaminophen remains constant once the concentration in the liver increases above a saturation level. A schematic of acetaminophen metabolism is shown in Figure 2.

The major metabolic pathway is glucuronidation, where 47% to 62% of the acetaminophen dose conjugates with glucuronide. These glucuronide conjugates are inactive and nontoxic, and are secreted in bile and eliminated in the urine. The second major pathway is sulfation, where 25% to 36% of the dose conjugates with sulfate. These sulfate ester conjugates are also inactive and nontoxic and are excreted in the urine. The third pathway is oxidation, where 5% to 8% of the dose is metabolized via the cytochrome P450 enzyme system. The cytochrome P450 isoenzyme that is primarily responsible is CYP2E1. When acetaminophen is metabolized by CYP2E1, it forms a highly reactive intermediate, N-acetyl-p-benzoquinoneimine (NAPQI). Since NAPQI is highly reactive, it cannot be measured outside the liver nor can it accumulate. This intermediate is rapidly inactivated by hepatocellular stores of glutathione to form cysteine and mercapturate conjugates, which are both inactive and nontoxic. These conjugates are excreted in the urine.

Figure 2: Acetaminophen Metabolism



Elimination

Acetaminophen undergoes first-order elimination from the body, and has a short plasma half-life that ranges from 2 to 3 hours in healthy young and elderly adults and from 1.5 to 2.9 hours in children (Miners 1988, Triggs 1975, Briant 1976, Divoll 1982, Bedjaoui 1984, Bannwarth 1992, Nahata 1984, Walson 1989, Brown 1992, Kelley 1992, Rømsing 2001). Since acetaminophen clears rapidly from the body, repeated doses do not lead to accumulation of acetaminophen plasma concentrations.

Diphenhydramine Hydrochloride

Diphenhydramine peak plasma concentrations occur in 2-3 hours and are similar in young and elderly healthy men and women while diphenhydramine half-life is somewhat longer and more variable in elderly men. The pharmacokinetics of diphenhydramine are affected by ethnic origin, the mean plasma levels of diphenhydramine are lower in Asians compared to Caucasians.

Furthermore, greater tissue distribution (V_d : 480 versus 292 L/70 kg) and faster drug clearances (79 versus 51 L/70 kg/hr) are seen in Asians compared to Caucasians. Nonrenal clearance (around 33 L/h) is the major contributor to the overall clearance (Cl/F approximately 45 L/h) of diphenhydramine with the renal clearance of unchanged drug contributing only about 1 L/h. The oral bioavailability of diphenhydramine ranges from 43 to 72 %.

Diphenhydramine is highly lipophilic and easily crosses the blood-brain barrier causing sedation. Due to its lipophilic character, diphenhydramine also undergoes extensive hepatic metabolism.

Diphenhydramine is rapidly and almost completely metabolized in the liver, by demethylation, principally to diphenylmethoxyacetic acid. Low circulating plasma concentrations of antihistamines are in part explained by significant first-pass effect and tissue distribution.

Diphenhydramine inhibits CYP2D6 leading to a clinically significant drug-drug interaction when co-administered with compounds that likewise require metabolism via cytochrome P450, such as

metoprolol, tricyclic antidepressants, antiarrhythmic drugs, antipsychotics and tramadol (Sharma 2003, Bartra 2006).

Special Populations and Conditions

- **Genetic Polymorphism:** Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency: In therapeutic doses, acetaminophen does not shorten the lifespan of red blood cells and does not produce any clinically perceptible destruction of circulating red blood cells (Chan 1976, Cottafava.1990, Beutler 1984).
- **Hepatic Insufficiency:** Slower metabolism of acetaminophen, increased activity of the cytochrome P450 enzyme system, or depleted glutathione stores are cited as theoretical risk factors for acetaminophen hepatotoxicity in patients with chronic liver disease. However, acetaminophen has been studied in both adults and children with a wide variety of liver diseases including various types of cirrhosis, hepatitis (including hepatitis C), nodular transformation, congenital hepatic fibrosis, and α 1-antitrypsin deficiency. In none of these conditions is there evidence of an increased risk for hepatotoxicity at currently recommended acetaminophen doses but the studies were insufficiently powered to definitely establish the extent of risk [See **7 WARNINGS AND PRECAUTIONS**].
- **Renal Insufficiency:** Based on available clinical data, acetaminophen can be used in patients with chronic renal disease without dosage adjustment. Martin et al (1991) found that patients with chronic renal failure had higher plasma concentrations of acetaminophen and the inactive glucuronide and sulfate metabolites than healthy subjects during repeated dosing up to ten days.

Several single-dose studies demonstrate accumulation of acetaminophen metabolites in patients with moderate chronic renal failure and in anephric patients for whom hemodialysis appeared to be the major route of elimination (Lowenthal 1976, Chan 1997, Prescott 1989, Øie 1975) [See **7 WARNINGS AND PRECAUTIONS**].

- **Obesity:** Results of well-designed clinical studies indicate that a dose reduction of acetaminophen, to avoid potential increased risk for toxicity, is not necessary. O'Shea et al (1994) studied the pharmacokinetics of chlorzoxazone (a putative probe for CYP2E1 activity) to evaluate the effect of obesity on CYP2E1 activity. The authors concluded that CYP2E1 is induced in obese adults and that this could impact the metabolic pathway of a number of drugs metabolized by CYP2E1, including acetaminophen. However, acetaminophen pharmacokinetic data have been investigated in obese adults (Abernethy 1982). In this prospective study, 650 mg acetaminophen was administered intravenously to obese men (297 lb), obese women (194 lb), control men (155 lb) and control women (121 lb). Acetaminophen distribution volume per total body weight was slightly lower in the obese adults but, more importantly, the half-life and metabolic clearance per total body weight did not differ among groups.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 to 30°C).

PART II: SCIENTIFIC INFORMATION

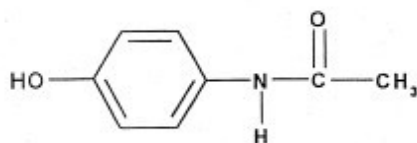
13 PHARMACEUTICAL INFORMATION

Drug Substance – Acetaminophen

Proper name: Acetaminophen

Chemical name: N-acetyl-p-aminophenol

Molecular formula and molecular mass: C₈H₉NO₂/ 151.16



Structural formula:

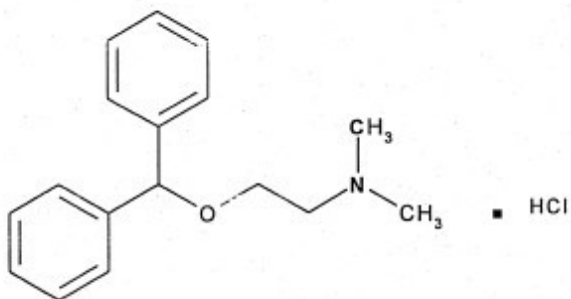
Physicochemical properties: Acetaminophen is a white, crystalline powder soluble in methanol, ethanol, DMF, acetone, ethyl acetate; very slightly soluble in cold, more so in hot water.

Drug Substance – Diphenhydramine Hydrochloride

Proper name: Diphenhydramine Hydrochloride

Chemical name: 2-Diphenylmethoxy-N,N-dimethylethanamine HCl

Molecular formula and molecular mass: C₁₇H₂₁NO / 291.41



Structural formula:

Physicochemical properties: Diphenhydramine Hydrochloride is a white to off-white crystalline powder soluble in water, alcohol, chloroform, acetone; very slightly soluble in benzene, ether.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Two randomized, double-blind, placebo-controlled, single-dose, parallel-group studies (Studies AADPWS4002 and AADPWS4001) were conducted to evaluate the effects of acetaminophen and diphenhydramine hydrochloride, in combination and separately, versus placebo on sleep in subjects post-oral surgery with phase-shifted sleep. The two studies were very similar in design. Table 6 summarizes the clinical trial designs and highlights the main differences.

Table 6: Summary of Clinical Design

Study ID	Trial Design	Study & Ctrl Drugs: Dose, Route	Study Subjects Mean age (range)	Main Inclusion Criteria	Phase-shifted sleep interval
AADPWS4002	Randomized, double-blind, placebo-controlled, parallel-group, single dose	APAP/DPH caplets: 2 x APAP500 mg /DPH25 mg, oral APAP caplets: 2 x 500 mg, oral DPH capsules: 2 x 25 mg, oral APAP Placebo caplet: 2 inert caplets, oral DPH Placebo capsules: 2 inert capsules, oral	338 18.2 yrs (16 – 45yrs)	Subjects experiencing mild, moderate or severe post-surgical pain after surgical extraction of up to 2 third molars including only one mandibular third molar at least partially impacted	At least 5 hours earlier than usual

AADPWS4001	Randomized, double-blind, placebo-controlled, parallel-group, single dose	APAP/ DPH caplets: 2 x APAP500 mg /DPH25 mg, oral APAP caplets: 2 x 500 mg, oral Placebo caplets: 2 inert caplets, oral	85 19.5 yrs (16 – 45 yrs)	Subjects experiencing mild, moderate or severe post-operative pain after surgical extraction of 1- 2 third molars including only one mandibular third molar at least partially impacted	At least 5 hours earlier than usual
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The primary efficacy endpoint of both studies was total sleep time, as assessed by actigraphy. Secondary endpoints included global assessment of study medication as a sleep-aid, wake after sleep onset, sleep latency, global assessment of study medication as a pain reliever, and time to rescue in minutes. Subjective assessments of sleep refreshment and sleep quality were also performed.

14.2 Study Results

Results from Study AADPWS4002 and AADPWS4001 indicate that, for the pain and sleep variables measured, the combination of acetaminophen 1000 mg and diphenhydramine hydrochloride 50 mg provided significantly greater relief than placebo for dental pain ($p < 0.001$, Studies AADPWS4002, AADPWS4001) and sleeplessness (total sleep time: $p < 0.001$, Studies AADPWS4002, AADPWS4001). Studies AADPWS4002 and AADPWS4001 also demonstrated that the combination of acetaminophen 1000 mg and diphenhydramine hydrochloride 50 mg provided statistically greater relief of sleeplessness when compared with acetaminophen 1000 mg alone ($p = 0.001$, Study AADPWS4002; $p = 0.003$, Study AADPWS4001).

Study AADPWS4002

The study results demonstrated the significant individual contributions of both acetaminophen and diphenhydramine hydrochloride to the analgesic/sleep aid combination product. In addition, this study demonstrated the incremental statistically significant benefit of diphenhydramine hydrochloride, a sleep aid, when combined with acetaminophen, a pain reliever, in subjects with pain and sleeplessness. Acetaminophen 1000 mg in combination with diphenhydramine hydrochloride 50 mg provided statistically significantly greater relief of sleeplessness when compared with acetaminophen 1000 mg alone, diphenhydramine hydrochloride 50 mg alone, and placebo, and provided statistically significantly greater relief of dental pain when compared with diphenhydramine hydrochloride and placebo.

The least squares mean total sleep times were 287.31 minutes for subjects treated with the combination of acetaminophen 1000 mg/diphenhydramine hydrochloride 50 mg, 226.37 minutes for

subjects treated with acetaminophen 1000 mg, 174.57 minutes for subjects treated with diphenhydramine hydrochloride 50 mg, and 63.12 minutes for subjects treated with placebo.

Total sleep time was statistically significantly longer for subjects treated with the combination of acetaminophen 1000 mg/diphenhydramine hydrochloride 50 mg compared with subjects treated with acetaminophen 1000 mg ($p = 0.001$), diphenhydramine hydrochloride 50 mg ($p < 0.001$), and placebo ($p < 0.001$). In addition, total sleep time was statistically significantly longer for subjects treated with acetaminophen 1000 mg compared with those treated with placebo ($p < 0.001$), and marginally significantly longer compared with those treated with diphenhydramine hydrochloride 50 mg ($p = 0.053$). Total sleep time was also statistically significantly longer for subjects treated with diphenhydramine hydrochloride 50 mg compared with those treated with placebo ($p < 0.001$). These results demonstrate the statistically significant incremental benefit of diphenhydramine hydrochloride in combination with acetaminophen compared with acetaminophen alone in relief of sleeplessness in this study.

The global assessment of study medication as a pain reliever was the primary assessment of pain relief. The least squares mean global assessment of study medication as a pain reliever were

1.66 for subjects treated with the combination of acetaminophen 1000 mg/diphenhydramine hydrochloride 50 mg, 0.99 for subjects treated with diphenhydramine hydrochloride 50 mg, 1.77 for subjects treated with acetaminophen 1000 mg, and 0.40 for subjects treated with placebo. The global assessment was statistically significantly greater for subjects treated with the combination of acetaminophen 1000 mg/diphenhydramine hydrochloride 50 mg compared with those treated with diphenhydramine hydrochloride 50 mg ($p < 0.001$), and compared with those treated with placebo ($p < 0.001$). These results demonstrate the statistically significant benefit of acetaminophen in pain relief in this study.

Study AADPWS4001

Overall the results demonstrated that the combination of acetaminophen 1000 mg with diphenhydramine hydrochloride 50 mg provided statistically significantly greater relief of sleeplessness when compared with acetaminophen 1000 mg alone and compared with placebo, and provided statistically significantly greater relief of dental pain when compared with placebo. The results also show that the presence of diphenhydramine hydrochloride conferred a statistically significant incremental benefit when in combination with acetaminophen compared with acetaminophen alone in relief of sleeplessness.

The protocol-specified primary endpoint was total sleep time, as objectively assessed by actigraphy. The least squares mean total sleep times were 359.96 minutes for subjects treated with the combination of acetaminophen 1000 mg/diphenhydramine hydrochloride 50 mg, 252.30 minutes for subjects treated with acetaminophen 1000 mg, and 127.37 minutes for subjects treated with placebo. Total sleep time was statistically significantly longer for subjects treated with the combination of acetaminophen 1000 mg/diphenhydramine hydrochloride 50 mg compared with those treated with acetaminophen 1000 mg ($p = 0.003$) and compared with those treated with placebo ($p < 0.001$). In addition, total sleep time was statistically significantly longer for subjects treated with acetaminophen 1000 mg compared with those treated with placebo ($p = 0.013$). These results demonstrate the statistically significant incremental

benefit of diphenhydramine hydrochloride in combination with acetaminophen compared with acetaminophen alone in relief of sleeplessness in this study.

The global assessment of study medication as a pain reliever was the primary assessment of pain relief. The least squares mean global assessment of study medication as a pain reliever were 2.00 for subjects treated with the combination of acetaminophen 1000 mg/diphenhydramine hydrochloride 50 mg, 1.77 for subjects treated with acetaminophen 1000 mg, and 0.37 for subjects treated with placebo. The global assessment was statistically significantly greater for subjects treated with the combination of acetaminophen 1000 mg/diphenhydramine hydrochloride 50 mg compared with those treated with placebo ($p < 0.001$). These results demonstrate the statistically significant benefit of acetaminophen in pain relief in this study.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

14-Day Toxicity Studies

Acetaminophen

Fourteen-day toxicity studies in F344/N rats, showed acetaminophen in the diet was well tolerated by rats following oral administration of 0, 800, 1600, 3100, 6200 or 12500 ppm, for 14 days. Similarly, toxicity studies in B6C3F1 mice showed that acetaminophen was well tolerated by the mice following administration of 0, 250, 500, 1000, 2000 or 4000 ppm for 14 days. All animals survived until the end of the study. No compound related lesions were found at necropsy (National Toxicology Program 394).

Diphenhydramine Hydrochloride

In F344/N rats, oral doses of 0, 620, 1250, 2500, 5000 or 10000 ppm diphenhydramine hydrochloride in the diet were administered for 14 consecutive days. All rats in the 10000 ppm group and 9/10 rats in the 5000 ppm group died before the end of the studies. In B6C3F1 mice administered 0, 310, 620, 1250, 2500 or 5000 ppm diphenhydramine hydrochloride showed that all animals in the 5000 ppm group, 4 animals per sex in the 2500 ppm group and 4 male animals in the 1250 ppm group died before the end of studies (National Toxicology Program 355).

13-Week Toxicity Studies

Acetaminophen

Repeat dose toxicity studies were carried out for 13 weeks on F344/N rats and B6C3F1 mice administered 0, 800, 1600, 3200, 6400, 12500 or 25000 ppm acetaminophen in the diet. In the 25000 ppm group, chronic active liver inflammation of mild to moderate severity and acetaminophen related minimal tubular regeneration was seen in the kidneys of all animals.

Similarly, in the 25000 ppm group, all male rats exhibited testicular atrophy while the female rats had

atrophy of the uterus and ovary (National Toxicology Program 394).

Diphenhydramine Hydrochloride

In 13-week studies in F344/N rats, administered 0, 156, 313, 625, 1250 and 2500 ppm diphenhydramine hydrochloride in the diet, cytoplasmic vacuolization of the liver was found in all animals from 313 ppm dosage upwards. B6C3F1 mice, administered 0, 78, 156, 313, 625 and 1250 ppm of diphenhydramine hydrochloride in the diet, showed no compound-related histopathologic effects (National Toxicology Program 355).

Carcinogenicity:

Acetaminophen

Carcinogenicity studies for 2 years (103 weeks) duration were included in F344/N rats and B6C3F1 mice administered 0, 600, 3000 or 6000 ppm acetaminophen in the feed. There was no evidence of carcinogenicity of acetaminophen in male and female B6C3F1 mice in all the dose groups. Similarly there was no evidence of acetaminophen carcinogenicity in the male rats in the 600, 3000 or 6000 ppm groups whereas the female rats showed equivocal increased incidences of mononuclear cell leukemia, with higher dosage (National Toxicology Program 394).

Diphenhydramine Hydrochloride

Long term carcinogenicity studies were performed in male F344/N rats administered 0, 313 or 625 ppm, and in B6C3F1 male and female mice as well as female rats administered 0, 156 or 313 ppm diphenhydramine hydrochloride for 103 weeks in the diet. The incidence of glial cell tumors in the high dose male rats and alveolar / bronchiolar adenomas in low dose male rats was slightly greater than in the controls. Female rats showed significant incidences of adenomas in the anterior pituitary gland. However, incidences of neoplastic lesions were not considered to be compound related. There was also no evidence of carcinogenicity in mice (National Toxicology Program 355).

Genotoxicity:

Acetaminophen

Acetaminophen genotoxicity studies were done in *S. typhimurium* strains TA100, TA102, TA1535, TA1537 or TA98 with or without S9. There was no evidence of mutagenicity in these tests (National Toxicology Program 394, Rannug 1995). Cytogenicity tests with Chinese Hamster ovary cells showed that acetaminophen induced sister chromatid exchanges and chromosomal aberrations both in the presence and absence of S9. In the sister chromatid test, positive responses were observed over a concentration range of 5-150 µg/mL in the absence of S9 whereas in the presence of S9, only the highest dose 5000 µg/mL produced a significant increase in the sister chromatid exchanges. In the chromosomal aberration test without S9, acetaminophen concentrations of 1257-5000 µg/mL produced significant increases in the percentage of aberrant cells (National Toxicology Program 394).

Diphenhydramine Hydrochloride

Diphenhydramine hydrochloride did not show any mutagenic potential in genotoxicity tests. *S. typhimurium* strains TA98, TA100, TA1535 or TA1537 did not exhibit positive results for mutagenicity when tested in the presence or absence of metabolic activation. In cytogenetic tests with Chinese

Hamster ovary cells, chromosomal aberrations were not observed in the presence of metabolic activation (S9) but were induced in the absence of metabolic activation (S9). There was no induction of sister chromatid exchanges with or without S9. These studies established that diphenhydramine hydrochloride is not genotoxic (National Toxicology Program 355).

Reproductive and Developmental Toxicology:

Acetaminophen

For reproductive toxicity analysis, Lamb et al (1997) tested acetaminophen for its effects on reproduction and fertility in CD-1 mice, following the RACB protocol (Reel 1992). The toxicity produced by acetaminophen in the diet of Swiss mice was on the growing neonate. Fertility end points (ability to bear normal numbers of normal-weight young) were generally not affected (Lamb 1997).

Diphenhydramine Hydrochloride

Teratologic studies in timed-pregnant CD[®] rats, administered 0, 25, 50 or 100 mg/ kg per day diphenhydramine hydrochloride on gestational days 6 through 15 showed that maternal body weight gain was lower in the high dose group than the controls. Teratology studies performed in CD[®] -1 mice, administered 0, 40, 80 or 160 mg/kg diphenhydramine hydrochloride per day on days 6 through 15 of gestation showed no dose related resorptions, dead or malformed fetuses, but an increased incidence of cleft palate was observed with higher doses (National Toxicology Program 355).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

EXTRA STRENGTH TYLENOL® NIGHTTIME

Acetaminophen and Diphenhydramine Hydrochloride Caplets

Read this carefully before you start taking **EXTRA STRENGTH TYLENOL® NIGHTTIME** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **EXTRA STRENGTH TYLENOL® NIGHTTIME**.

Serious Warnings and Precautions

- Causes sedation or sleepiness. Not for daytime use.
- Do not take more than the maximum daily dose. Overdose may result in severe or possibly fatal liver damage.

What is EXTRA STRENGTH TYLENOL® NIGHTTIME used for?

- Extra Strength TYLENOL® Nighttime provides fast and effective relief of occasional mild to moderate nighttime pain and accompanying sleeplessness due to: back and body pain, headaches, muscle aches and pains, arthritis pain, menstrual pain, dental pain and aches and pains due to colds and the flu.
- Helps improve the duration of your sleep.

How does EXTRA STRENGTH TYLENOL® NIGHTTIME work?

Extra Strength TYLENOL® Nighttime contains two drugs: Acetaminophen (a pain reliever) and diphenhydramine hydrochloride (a sleep aid for sleeplessness). Pain relief from acetaminophen helps you fall asleep and diphenhydramine hydrochloride helps you stay asleep.

What are the ingredients in EXTRA STRENGTH TYLENOL® NIGHTTIME?

Medicinal ingredients: Acetaminophen 500 mg, Diphenhydramine Hydrochloride 25 mg

Non-medicinal ingredients: Carnauba wax, cellulose, corn starch, FD&C blue no.1 aluminum lake, hypromellose, magnesium stearate, polyethylene glycol, polysorbate 80, sodium citrate, sodium starch glycolate, titanium dioxide.

EXTRA STRENGTH TYLENOL® NIGHTTIME comes in the following dosage forms:

EXTRA STRENGTH TYLENOL® NIGHTTIME caplets are a combination of 500 mg of acetaminophen (extra strength) and 25 mg of diphenhydramine hydrochloride, which is available as light blue coloured caplets.


Do not use EXTRA STRENGTH TYLENOL® NIGHTTIME if:

- You are taking any other drug containing acetaminophen or diphenhydramine, even one used on the skin
- You have pain that does not keep you from sleeping
- You have sleeplessness but are not in pain
- You are allergic to acetaminophen, diphenhydramine hydrochloride or any of the other ingredients in this product. If you are not sure whether a drug contains acetaminophen or diphenhydramine, ask a doctor or pharmacist
- In children under 16 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EXTRA STRENGTH TYLENOL® NIGHTTIME Talk about any health conditions or problems you may have, including if you:

- Have serious kidney or liver disease
- Have chronic lung disease (including acute or chronic bronchial asthma, emphysema or chronic bronchitis), glaucoma, or difficulty in urination due to enlargement of the prostate gland
- Are pregnant or breastfeeding
- Are elderly and experience confusion at night, as this drug may cause excitation rather than sedation
- Use any other medications including the blood thinning drug warfarin, sedatives or tranquilizers or other pain and fever relief medications
- Have peptic ulcer

Other warnings you should know about:

 **KEEP OUT OF THE REACH OF CHILDREN.** This package contains enough drug to seriously harm a child. Use only on the advice of a doctor.

Liver warning: Acetaminophen may cause **severe or possibly fatal liver damage** if you take:

- more than the recommended dose in 24 hours;
- with other drugs containing acetaminophen;
- while drinking 3 or more alcoholic drinks every day.

Symptoms of liver damage may include:

- yellow skin or eyes, dark urine;
- sweating, nausea, vomiting, stomach pain;
- unusual tiredness, and/or loss of appetite.

Allergy alert: acetaminophen may cause serious skin reactions. Symptoms may include:

- skin reddening, blisters, rash

If any of these symptoms occur, stop use and seek medical help right away.

May cause marked drowsiness or excitability. Alcohol, sedatives and tranquilizers may increase drowsiness. Do not drive a motor vehicle, operate machinery or engage in activities requiring alertness when using this product. Avoid alcohol.

Stop use and ask a doctor if sleeplessness due to mild to moderate pain lasts for more than 5 days, if new symptoms appear or existing symptoms worsen. Sleeplessness may be a symptom of serious underlying medical illness.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with EXTRA STRENGTH TYLENOL® NIGHTTIME:

- Antihistamines, tranquilizers, alcohol or other sedating drugs
- Medications for depression, including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants and antipsychotics
- Medications for blood pressure, including metoprolol and antiarrhythmic drugs
- Opioid analgesic (e.g. tramadol)
- Other pain relievers, sleep aids or cold medicines
- Warfarin type anticoagulants and coumarin derivatives

How to take EXTRA STRENGTH TYLENOL® NIGHTTIME:

Usual dose:

Adult use only (16 years and older): Take 2 Extra Strength TYLENOL® Nighttime caplets at bedtime, or as directed by a doctor. Do not take more than 2 caplets in 24 hours.

Overdose:

If you think you, or a person you are caring for, have taken too much EXTRA STRENGTH TYLENOL® NIGHTTIME, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Take once at night before bedtime. Do not take twice the recommended dose after a missed dose.

What are possible side effects from using EXTRA STRENGTH TYLENOL® NIGHTTIME?

These are not all the possible side effects you may have when taking EXTRA STRENGTH TYLENOL® NIGHTTIME. If you experience any side effects not listed here, tell your healthcare professional.

You may experience drowsiness, dizziness, dryness of mouth, nausea and nervousness. Other side effects may include rapid heartbeat, blurred vision, headache, restlessness or excitability, sensation of disorientation or motion, sleeplessness and production of thick mucus.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY RARE			
Allergic reactions such as itching, blisters, rashes, skin reddening etc.			✓
Any change in vision, hallucinations, or difficulty speaking			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store caplets at 15 to 30°C.

Keep out of reach and sight of children.

If you want more information about EXTRA STRENGTH TYLENOL® NIGHTTIME:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.tylenol.ca, or by calling 1-800-265-7323.

This leaflet was prepared by McNeil Consumer Healthcare, division of Johnson and Johnson Inc.

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