PRODUCT MONOGRAPH

ABENOL

(acetaminophen)

120mg, 325 mg and 650 mg Suppositories

Analgesic, Antipyretic

PENDOPHARM INC.
8580, Esplanade
Montréal, Québec
H2P 2R8

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THERAPEUTIC CLASSIFICATION

Analgesic, Antipyretic

ACTIONS AND CLINICAL PHARMACOLOGY

Acetaminophen is the major metabolite of phenacetin and acetanilide. Animal and clinical studies have shown acetaminophen to have antipyretic and analgesic activity equal to that of acetylsalicylic acid. Acetaminophen lacks anti-inflammatory effects.

Unlike the salicylates, acetaminophen does not interfere with tubular secretion of uric acid nor does it affect acid-base balance if taken in therapeutic doses. Acetaminophen does not interfere with homeostasis and, in particular does not inhibit platelet aggregation. Allergic reactions are rare and thus the drug is useful in patients who cannot tolerate salicylates and those with an allergic diathesis, including bronchial asthmatics. The rate of acetaminophen absorption from the gastrointestinal tract following oral administration is a function of stomach emptying rate and is generally rapid and complete with peak plasma concentrations of free drug being achieved in 0.5 to 1 hour following administration. The plasma half-life of unchanged drug is about 2 hours with approximately 85% of a 1 g oral dose being recovered in the urine in 24 hours. Approximately 3% is excreted unchanged with the balance being eliminated principally as the glucuronide and sulfate conjugates. A small portion of the administered acetaminophen is converted by hepatic

microsomal enzymes to a reactive metabolite. At therapeutic doses this minor metabolite is rapidly inactivated by conjugation with glutathione and eliminated by renal excretion. However, where hepatic glutathione has been depleted, covalent binding of the reactive metabolite to liver-cell macromolecules occurs and hepatic cell necrosis ensues. It has been shown that glutathione precursors such as N-acetylcysteine, cysteine, cysteamine and methionine can decrease experimental acetaminophen - induced hepatic necrosis when administered promptly after a toxic dose of acetaminophen. Rectal absorption of ABENOL (acetaminophen), as with most rectally administered drugs, is more erratic than absorption following oral administration. Absorption rate is generally slower. Peak blood levels of free ABENOL are not reached until 1.5 - 3 hours following rectal administration and the peak concentration in the blood is approximately 50% of that observed following an equivalent oral dose. The percentage of a rectal dose of ABENOL absorbed also varies giving wide variances in the bioavailability. In view of these observations higher rectal doses or more frequent administration may be required to achieve and/or maintain blood concentrations of ABENOL comparable to those obtained following oral administration.

INDICATIONS AND CLINICAL USE

ABENOL (acetaminophen) is indicated for the treatment of mild to moderate pain and the reduction of fever.

CONTRAINDICATIONS

Hypersensitivity to acetaminophen or to its non-medicinal ingredients.

WARNINGS

Acetaminophen poisoning can result in severe hepatic damage.

PRECAUTIONS/ADVERSE REACTIONS

When used as directed, acetaminophen is virtually free of severe toxicity or side effects. The incidence of gastrointestinal upset is less than after salicylate administration. If a rare sensitivity reaction occurs, discontinue the drug. Hypersensitivity to acetaminophen is usually manifested by a rash or urticaria.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdose:

Overdose in adults: Hepatotoxicity may occur after ingestion of a single dose of 10 to 15 g (200 to 250 mg/kg) of acetaminophen, a dose of 25 g or more is potentially fatal. In adults, non-fatal overdoses (ranging from 12.5 to 31.5 g) have been reported and 1 death after 30 g of acetaminophen had been ingested. A 13-year-old child is reported to have died after ingesting 15g.

Symptoms:

Symptoms during the first 2 days of acute poisoning by acetaminophen do not reflect the potential seriousness of the intoxication. Nausea, vomiting, anorexia and abdominal pain occur during the initial 24 hours and may persist for a week or more. Liver injury may become manifest the second day, initially by elevation of serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of prothrombin time. Alkaline phosphatase activity and serum albumin concentration may remain normal. The hepatotoxicity may progress to encephalopathy, coma and death. Liver biopsy reveals centrilobular necrosis with sparing of the periportal area. In nonfatal cases, the hepatic lesions are reversible over a period of weeks or months. Transient azotemia is apparent in most patients and acute renal failure occurs in some. Hypoglycemia may occur, but glycosuria and impaired glucose tolerance have also been reported. Both metabolic acidosis and metabolic alkalosis have been noted, cerebral edema and non-specific myocardial depression have also occurred. Since acetaminophen is metabolized primarily by the liver, in cases of acute poisoning, prolongation of the plasma half-life beyond 3 hours may be indicative

of liver injury. Hepatic necrosis should be anticipated if the half-life exceeds 4 hours, and hepatic coma is likely if the half-life is greater than 12 hours. A single determination of serum acetaminophen concentration is a less reliable predictor of hepatic injury. However, only minimal liver damage has developed when the serum concentration was below 120 μg/mL at 4 hours or less than 50 μg/mL at 12 hours after ingestion of the drug. Encephalopathy should also be anticipated if serum bilirubin concentration exceeds 4 mg/100 mL during the first 5 days.

Treatment

Early diagnosis is vital in the treatment of overdose with acetaminophen. Vigorous supportive therapy is essential when intoxication is severe. Procedures to limit continuing absorption of the drug must be initiated promptly. When the oral route of administration is used induction of vomiting or gastric lavage should be performed and should be followed by oral administration of activated charcoal (50 g). Hemodialysis, if it can be initiated within the first 12 hours, has been advocated for all patients with a plasma concentration of acetaminophen greater than 120 μg/mL 4 hours after drug ingestion. If administered within the first few hours after ingestion of acetaminophen, sulphydryl compounds, which replete glutathione, have been shown to effectively prevent or reduce the hepatotoxic effects of acetaminophen. N-acetylcysteine, available commercially as a sterile 20% solution (MUCOMYST®) has been shown to be particularly effective and well tolerated when given orally as a 5% solution diluted with cola, fruit juice, or water. The accepted treatment regimen is a loading dose of 140 mg/kg followed by 70 mg/kg every 4 hours for 17 doses or until plasma concentrations of acetaminophen are indicative of a low risk to hepatotoxicity.

DOSAGE AND ADMINISTRATION

Adults: 650 mg every 4 to 6 hours as necessary. Maximum daily recommended is 6 suppositories.

Children:

Under 2 years:	As recommended by the physician.
2 to 4 years:	120 mg every 4 hours. Maximum daily dosage recommended is 6 suppositories.
4 to 6 years:	325 mg every 6 hours. Maximum daily dosage recommended is 4 suppositories.
6 to 12 years:	325 mg every 4 hours. Maximum daily dosage recommended is 6 suppositories.

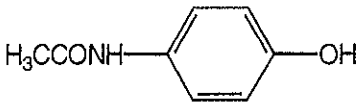
A physician should be consulted for treatment regimens lasting longer than 5 days. Inherent in the rectal route of administration is the possibility of erratic absorption, lower blood concentrations and lower bioavailability in some patients relative to the oral route. Therefore more frequent rectal administration is acceptable when deemed necessary by the prescriber.

PHARMACEUTICAL INFORMATION

Drug Substance:

Chemical Name: N-(4-Hydroxyphenyl) acetamide

Structural Formula:



Empirical Formula: $C_8H_9NO_2$

Molecular Weight: 151.16

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

Composition:

Each suppository contains acetaminophen as the medicinal ingredient and has the following non-medicinal ingredient; Novata.

Storage Recommendations: Store at room temperature.

AVAILABILITY OF DOSAGE FORMS

ABENOL120 mg: Each white smooth torpedo shaped suppository contains 120 mg of acetaminophen.

ABENOL325 mg: Each white smooth torpedo shaped suppository contains 325 mg of acetaminophen.

ABENOL650 mg: Each white smooth torpedo shaped suppository contains 650 mg of acetaminophen

Available in cartons containing 4 or 12 individually sealed suppositories.

INFORMATION FOR THE CONSUMER

This information is also intended to be used separately as a Consumer Insert.

ABENOL

(Acetaminophen Suppositories USP)

Supplementary Information

FOR RECTAL USE ONLY.

Indications

ABENOL suppositories are used to relieve mild to moderate pain, and to reduce fever.

Instructions

- Wash hands with soap and water.
- Remove foil wrapper.
- Moisten suppository with cool water.
- Lie on side with bottom leg straight and upper leg bent up towards chest.
- Gently push suppository as high as possible into rectum.
- Wash hands with soap and water.

Dosage

Adults: 1 suppository (650 mg) every 4 to 6 hours as necessary. Do not use immediately before bowel movement. Maximum daily dosage is 6 suppositories.

Children: Under 2 years: As recommended by physician. 2 to 4 years: 1 suppository (120 mg) every 4 hours. Maximum daily dosage is 6 suppositories. 4 to 6 years: 1 suppository (325 mg) every 6 hours. Maximum daily dosage is 4 suppositories. 6 to 12 years: 1 suppository (325 mg) every 4 hours. Maximum daily dosage is 6 suppositories.

Drug interactions

Use of acetaminophen together with an anticoagulant may increase the time necessary for blood to coagulate. A physician or pharmacist should be consulted prior to using this medication in case of :

- allergy to acetaminophen, chronic alcoholism, kidney or liver disease; and
- intake of other medications containing acetaminophen or salicylates.

Adverse effects

Rare instances of hypersensitivity to acetaminophen are usually manifested by a rash or urticaria (hives).

Treatment of Overdosage

In the event of accidental ingestion of large quantities of suppositories, it is recommended to induce vomiting and to consult a physician.

Caution

Consult your physician if symptoms persist after more than 5 days of treatment. Do not exceed the recommended dosage unless advised by a physician, since excessive dosage may cause liver damage.

Storage

Store at room temperature

PENDOPHARM INC.

Montreal, CANADA, H2P 2R8

TOXICOLOGY

The oral LD_{50} for acetaminophen in rats is 4.4 g/kg. The fatal dose for man is unknown. An 18-month-old child and a 3-year-old child each ingested 3 g of acetaminophen with no ill effects. One adult ingested 35 g and another 17.5 g, both recovered after developing symptoms and signs of hepatotoxicity. On the other hand, fatalities have been reported from large overdosages of 15, 25 and 75 g.

Although no direct evidence is available, pharmacokinetic studies would suggest that the susceptibility to hepatotoxicity of acetaminophen by the rectal route would be lower than that by the oral route.

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