PRODUCT MONOGRAPH

ACET 120

ACET 160

ACET 325

ACET 650

Acetaminophen Suppositories USP
120 mg, 160 mg, 325 mg, 650 mg

Analgesic / Antipyretic

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Date of Preparation:
July 19, 2017

Control # 204828

NAME

ACET 120 / ACET 160 / ACET 325 / ACET 650
(Acetaminophen Suppositories USP)
120 mg, 160 mg, 325 mg, 650 mg

THERAPEUTIC CLASSIFICATION

Analgesic / Antipyretic

ACTION AND CLINICAL PHARMACOLOGY

Acetaminophen is the major metabolite of phenacetin and acetanilid. 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 hemostasis 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 1/2 to 2 hours following administration.

With doses up to 650 mg the peak plasma concentrations are from 5 to 20 mcg/mL. The time to reach peak effect is 1 to 3 hours and the duration of action is 3 to 4 hours. The plasma half-life of unchanged drug is about 2 hrs with approximately 85% of a 1 gm oral dose being recovered in the urine in 24 hrs. Approximately 3% is excreted unchanged with the balance being eliminated principally as the glucoronide and sulfate conjugates.

A small portion of the administered acetaminophen is converted by hepatic microsomal enzymes to 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 acetaminophen, as with most rectally administered drugs, is more erratic than absorption following oral administration. Absorption rate is generally slower.

A double-blind, single dose, randomized, cross-over study was conducted on healthy adults (average weight 75.2 kg) to evaluate and compare the rate and extent of absorption and comparative bioavailability between ACET 120 (120 mg) suppository (test product), and ABENOL 120 mg suppository, a Canadian marketed formulation (reference product). Comparative bioavailability between formulations was evaluated on statistical comparison of areas under the plasma concentrations versus time curves (AUC's), peak concentrations (Cmax) and time to reach peak concentrations (Tmax).

The summary of the results obtained are as follows:

Results of Comparative Pharmacokinetic Study of Unchanged Acetaminophen in Blood Following Administration of 120 mg Suppositories

	Mean values (± CV%)	
	Reference Product	Test Product
Observed C_{MAX} (g/mL)	1.07 (31.5)	1.21 (21.4)
Observed T_{MAX} (h)	1.1 (37.4)	1.2 (25.5)
AUC_{CUM} (g.h/mL)	4.48 (29.8)	4.65 (20.4)
AUC (g.h/mL)	5.12 (32.1)	5.38 (25.6)
Ratio $AUC_{CUM/AUC}$ (%)	87.93 (4.7)	87.59 (7.7)
MRT (h)	3.0 (9.5)	3.0 (8.6)
Elimination $T_{1/2}$ (h-1)	3.1 (19.8)	3.3 (43.9)

AUC_{CUM} = Cumulative area under the plasma concentration time curve calculated from 0 to time of last quantifiable concentration.
MRT = Mean Residence Time

From this study, no statistical difference could be detected between the two formulations for all the pharmacokinetic parameters under study; the relative bioavailability was 106.4%.

A similar double-blind, single dose, randomized, cross-over study was conducted on healthy adults (average weight 74.3 kg) to evaluate and compare the rate and extent of absorption and comparative bioavailability between ACET 650 (650 mg) suppository (test product) and ABENOL 650 mg suppository, a Canadian marketed formulation (reference product). Comparative bioavailability between formulations was evaluated on statistical comparison of areas under the plasma concentrations versus time curves (AUCs), peak concentrations (Cmax) and time to reach peak concentrations (Tmax).

The summary of the results obtained are as follows:

Results of Comparative Pharmacokinetic Study of Unchanged Acetaminophen in Blood Following Administration of 650 mg Suppositories

Mean values (± CV%)

	Reference Product		Test Product	
Observed C_{MAX} (g/mL)	3.20	(26.9)	4.13	(28.1)
Observed T_{MAX} (h)	4.1	(50.3)	2.8	(65.2)
AUC_{CUM} (g.h/mL)	24.07	(27.1)	27.72	(28.9)
AUC (g.h/mL)	26.89	(30.8)	30.71	(28.5)
Ratio $AUC_{CUM/AUC}$ (%)	90.4	(5.4)	90.4	(5.9)
MRT (h)	5.6	(13.1)	5.2	(10.6)
Elimination $T_{1/2}$ (h-1)	7.0	(40.7)	6.1	(57.0)

AUC_{CUM} = Cumulative area under the plasma concentration time curve calculated from 0 to time of last quantifiable concentration.
MRT = Mean Residence Time

Peak blood levels of free acetaminophen are not reached until 3 hours following rectal administration of ACET Suppositories and the peak concentration in the blood is approximately 50% of that observed following an equivalent oral dose (10-20 mcg/mL).

The percentage of a rectal dose of acetaminophen 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 acetaminophen comparable to those obtained following oral administration. No adverse reactions were reported and all physical, medical and laboratory evaluations were judged to be clinically normal.

INDICATIONS AND CLINICAL USE

Acetaminophen is indicated for the treatment of mild to moderate pain and the reduction of fever.

CONTRAINDICATIONS

Hypersensitivity to acetaminophen.

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, usually manifested by a rash or urticaria, discontinue use of the drug.

Drug Interactions and/or Related Problems:

Risk of hepatotoxicity with single toxic doses or prolonged use of high doses of acetaminophen may be increased in alcoholics or in patients regularly taking other hepatotoxic medications or hepatic enzyme inducers.

Concurrent chronic high-dose administration of acetaminophen may increase the anticoagulant effect of anticoagulants, coumarin or andantino-derivative.

Prolonged concurrent use of acetaminophen and anti-inflammatory drugs, nonsteroidal (NSAIDs) or aspirin or other salicylates is not recommended because recent evidence suggests that chronic high-dose administration of combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, end-stage renal disease, and cancer of the kidney or urinary bladder.

Diflusinal may increase the plasma concentration of acetaminophen by 50%, leading to increased risk of acetaminophen-induced hepatotoxicity.

Acetaminophen may competitively inhibit the hepatic glucoronidation and decrease the clearance of zidovudine; zidovudine may also inhibit the hepatic glucoronidation of acetaminophen.

Diagnostic interference:

Acetaminophen may cause false measurements in blood glucose determinations.

Administration of acetaminophen prior to pancreatic function tests using bentiromide will invalidate test results.

Acetaminophen may cause falsely increased serum uric acid determinations when the phosphotungstate uric acid test method is used.

Acetaminophen may cause false positive results in qualitative screening tests of urine 5Bhydroxyindoleacetic acid (5-HIAA) determinations using nitrosonaphthol reagent.

In alcoholic patients taking hepatic enzyme inducers, or patients with pre-existing hepatic disease, when single toxic doses of acetaminophen are taken (or with prolonged use of lower doses), prothrombin time, serum bilirubin concentrations, serum lactate dehydrogenase activity, and serum transaminase activity may be increased.

Although the incidence of adverse effects is rare, the following adverse effects may have clinical significance (possible signs and symptoms in parentheses):

- Agranulocytosis (unexplained sore throat and fever)

- Anemia (unusual tiredness or weakness)

- Dermatitis, allergic (skin rash, hives, or itching)

- Hepatitis (yellow eyes or skin)

- Renal colic (pain, severe and/or sharp, in lower back and/or side) with prolonged use of high doses in patients with severe renal function impairment.

- Renal failure (sudden decrease in amount of urine):-uremia may result, especially with prolonged use of high doses in patients with severe renal function impairment; also although a causal association has not been established a retrospective study has suggested that long term daily use of acetaminophen may be associated with an increased risk of chronic renal disease (analgesic nephropathy) in individuals without pre-existing renal function impairment.

- Sterile pyuria (cloudy urine)

- Thrombocytopenia (usually asymptomatic: rarely, unusual bleeding or bruising; black, tarry stools; blood in urine or stools; pinpoint red spots on skin)

SYMPTOMS AND TREATMENT OF OVERDOSAGE:

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, cases of non-fatal overdose (ranging from 12.5 to 31.5 g) have been reported; and one death after ingestion of 30 g of acetaminophen has been reported. A 13 year old child is reported to have died after ingesting 15 g.

SYMPTOMS: The first 2 days of acute poisoning by acetaminophen do not reflect the potential seriousness of the intoxication, and hepatoxicity is generally believed to occur only with acute overdosage. 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 following oral ingestion, 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 following oral ingestion. 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 mcg/mL at 4 hours, or less than 50 mcg/mL at 12 hours after ingestion of the drug. Encephalopathy should 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 gm). Hemodialysis, if it can be initiated within the first 12 hrs, has been advocated for all patients with a plasma concentration of acetaminophen greater than 120 mcg/mL, 4 hrs after drug ingestion. If administered within the first few hours, ingestion of

sulphydryl compounds, which replenish glutathione, have been shown to effectively prevent or reduce the hepatotoxic effects of acetaminophen. N-acetylcysteine, available commercially as a sterile 20% solution 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 hrs for 17 doses or until plasma concentrations of acetaminophen are indicative of a low risk to hepatotoxicity.

DOSAGE AND ADMINISTRATION

Adults and Children over 12 years: One suppository (650 mg) every 4 - 6 hours. Maximum daily dosage is 6 suppositories.

Infants under 1 year: Use only on the advice of a physician.

Infants 1 to 2 years: One suppository (120 mg) every 4 hours. Maximum daily dosage is 5 suppositories.

Children 2 to 4 years: One suppository (160 mg) every 4 hours. Maximum daily dosage is 6 suppositories.

Children 4 to 6 years: One suppository (325 mg) every 6 hours. Maximum daily dosage is 4 suppositories.

Children 6 to 12 years: One suppository (325 mg) every 4 hours. Maximum daily dosage is 6 suppositories.

A physician should be consulted for treatment regimens lasting longer than 5 days.

The inherency in the rectal route of administration to an erratic absorption, lower blood concentrations and the possibility of lower bioavailability in some patients relative to the oral route of administration makes more frequent rectal administration acceptable when deemed necessary by the prescriber.

PHARMACEUTICAL INFORMATION

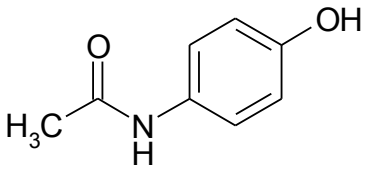
Name of the Drug Substance: Acetaminophen

Chemical Name: N-Acetyl-p-Aminophenol 4'-Hydroxyacetanilide
N-(4-Hydroxyphenyl) Acetamide

Molecular Weight: 151.2 g/mol

Molecular Formula: $C_8H_9NO_2$

Structural Formula:



Physiochemical properties: Acetaminophen is a white odourless crystalline powder with a slightly bitter taste. Soluble 1 in 70 of water, 1 in 20 in boiling water and, 1 in 7-10 in alcohol; very soluble in chloroform and ether.

AVAILABILITY OF DOSAGE FORMS

ACET 650 Suppositories

Each suppository, containing 650 mg acetaminophen, is individually sealed and available in boxes of 4 and 12.

ACET 325 Suppositories

Each suppository, containing 325 mg acetaminophen, is individually sealed and available in boxes of 4 and 12.

ACET 160 Suppositories

Each suppository, containing 160 mg acetaminophen, is individually sealed and available in boxes of 4 and 12.

ACET 120 Suppositories

Each suppository, containing 120 mg acetaminophen, is individually sealed and available in boxes of 4 and 12.

INFORMATION FOR THE CONSUMER

ACET 120 / ACET 160 / ACET 325 / ACET 650
(Acetaminophen Suppositories)

FOR RECTAL USE ONLY

Storage:
Store between 15°C and 25°C.

Indications:
ACET Suppositories are used to relieve mild to moderate pain, and to reduce fever.

Instructions:

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

Dosage:

Age (Years)	Single Dose	Maximum Daily Dose
Under 1	Use only on the advice of a physician.	
1 to 2	1 suppository (120 mg) every 4 hours	5 suppositoires
2 to 4	1 suppository (160 mg) every 4 hours	6 suppositoires
4 to 6	1 suppository (325 mg) every 6 hours	4 suppositoires
6 to 12	1 suppository (325 mg) every 4 hours	6 suppositoires
Over 12	1 suppository (650 mg) every 4 to 6 hours	6 suppositoires

Recommended non-pharmacological methods to manage fever:

- Adequate fluid intake
- Light clothing
- Body sponging with tepid water

Warnings:
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:

- Yellowing of the skin/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 or rash. **If any of the above noted symptoms occur, stop use and seek medical help right away.**

DO NOT USE:

- With other drugs containing **acetaminophen (**If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist)
- If you are allergic to acetaminophen or any other ingredient in this product

Ask a doctor before use if you:

- Have a liver or kidney disease

Ask doctor or pharmacist before use if you:

- Take the blood thinning drug warfarin
- Are pregnant or breastfeeding

Stop use and ask a doctor if:

- Condition persists for more than 5 days
- Fever lasts for more than 3 days

Keep out of reach of children. This package contains enough drug to seriously harm a child.

In case of overdose: Call a Poison Control Center or get medical help right away. Quick medical attention is critical even if you do not notice any signs or symptoms.

If emergency help is not available, vomiting should be induced at once (within 30 minutes) by ipecac syrup.
VOMITING SHOULD NEVER BE INDUCED IN UNCONSCIOUS INDIVIDUALS OR IN CHILDREN YOUNGER THAN 1 YEAR OLD WITHOUT MEDICAL HELP.

Signs of overdose: nausea or vomiting, stomach cramps or pain, and unusual increases in sweating, diarrhea, loss of appetite. Onset may be delayed 24 hours after intake.

TOXICOLOGY

The LD_{50} in mice has been reported to be 338 mg/kg orally and 500 mg/kg i.p. 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 and another 17.5 g, and both recovered after developing symptoms and signs of hepatotoxicity. On the other hand, fatalities have been reported from large overdosage of 15, 25 and 75 g.

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