PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# PrACETAMINOPHEN INJECTION

Acetaminophen Injection

Sterile solution for infusion, 10 mg/mL, intravenous

(Available as 100 mg/10 mL, 500 mg/50 mL and 1000 mg/100 mL)

Analgesic and Antipyretic

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## RECENT MAJOR LABEL CHANGES

None at time of authorization.

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**Sections or subsections that are not applicable at the time of authorization are not listed.**

## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

ACETAMINOPHEN INJECTION (acetaminophen injection) is indicated for the short term management and treatment of:

- mild to moderate pain
- moderate to severe pain with adjunctive opioid analgesics
- fever

ACETAMINOPHEN INJECTION may be given in single or repeated doses when an intravenous (IV) route of administration is considered clinically appropriate (see 4 DOSAGE AND ADMINISTRATION).

### 1.1 Pediatrics

**Pediatrics (≥ 2 years of age)**

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ACETAMINOPHEN INJECTION in pediatric patients ≥ 2 years of age has been established (see 7.1.3 Pediatrics and 14 CLINICAL TRIALS). Therefore, Health Canada has authorized an indication in patients ≥ 2 years of age for the short term management and treatment of:

- mild to moderate pain
- moderate to severe pain with adjunctive opioid analgesics
- fever

ACETAMINOPHEN INJECTION may be given in single or repeated doses when an IV route of administration is considered clinically appropriate (see 4 DOSAGE AND ADMINISTRATION).

**Pediatrics (< 2 years of age)**

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ACETAMINOPHEN INJECTION in pediatric patients < 2 years of age has not been established; therefore, Health Canada has not authorized an indication for this age group.

### 1.2 Geriatrics

ACETAMINOPHEN INJECTION is indicated for use in patients > 65 years of age. No dosage adjustments are required. However, as with other drugs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function (see 7 WARNINGS AND PRECAUTIONS and 7.1.4 Geriatrics).

## 2 CONTRAINDICATIONS

ACETAMINOPHEN INJECTION is contraindicated in

- patients who have previously demonstrated hypersensitivity to acetaminophen, 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.
- patients with severe hepatic impairment or severe active liver disease.

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

**Serious Warnings and Precautions**

Medication Errors
Caution is recommended when prescribing, preparing, and administering ACETAMINOPHEN INJECTION to avoid dosing errors which could result in accidental overdose and death (see 4 DOSAGE AND ADMINISTRATION and 5 OVERDOSAGE). In particular, ensure that:

- the dose in milligrams (mg) and milliliters (mL) is not confused;
- the dosing is based on weight for patients under 50 kg;
- infusion pumps are properly programmed; and
- the total daily dose of acetaminophen from all routes of administration (intravenous, oral and rectal) and all products containing acetaminophen (oral solutions/drops, syrup, pills, capsules, suppositories, etc.) does not exceed maximum daily limits.

Hepatotoxicity
Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the maximum daily limits, and often involve more than one acetaminophen-containing product (see 5 OVERDOSAGE and Hepatic/Biliary/Pancreatic).

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

The 10 ml ampoule is for use in pediatrics weighing up to 10 kg.
The 50 ml bottle is for use in pediatrics weighing more than 10 kg and up to 33 kg.
The 100 ml bottle is for use in adults, adolescents and children weighing more than 33 kg.
The dose to be administered and the container size to be used depend exclusively on the patient`s weight. The volume to be administered must not exceed the determined dose.

The maximum daily dose of acetaminophen includes all routes of administration (intravenous, oral and rectal) and all products containing acetaminophen (oral solutions/drops, syrup, pills, capsules, suppositories, etc.). Do not exceed the maximum recommended single/daily doses of acetaminophen described in Table 1.

- In order to avoid the risk of overdose, check that other medicines administered do not contain either acetaminophen or its prodrug. Adjust dose as required.
- Take care when prescribing and administering ACETAMINOPHEN INJECTION to avoid dosing errors due to confusion between milligram (mg) and millilitre (mL), which could result in accidental overdose and death. Ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume. Ensure the dose is measured and administered accurately.
- Prolonged or frequent use is discouraged. It is recommended that a suitable analgesic oral treatment be used as soon as this route of administration is possible.
- Caution is required when administering acetaminophen to patients with impaired hepatic

function, or those receiving medication that affects hepatic metabolism (e.g., enzyme inducing agents). In such cases, the clearance of acetaminophen may be reduced (see Hepatic/Biliary/Pancreatic and Hepatic Impairment).

- Caution is required when administering ACETAMINOPHEN INJECTION to patients presenting with chronic alcohol use (3 or more drinks/day), dehydration, malnutrition or other liver diseases. Rare cases of hepatotoxicity has occurred at or below recommended doses in patients with these risk factors. Monitoring liver function (AST or ALT) while administering ACETAMINOPHEN INJECTION should be considered in all patients where liver toxicity may be of concern.
- In patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) longer dosing intervals and/or a reduced total daily dose of acetaminophen may be warranted (see Renal and Renal Impairment).

ACETAMINOPHEN INJECTION reduces the febrile temperature set-point. Appropriate measures should be taken to allow adequate body heat dissipation.

### 4.2 Recommended Dose and Dosage Adjustment

No dose adjustment is required when converting between oral acetaminophen and intravenous acetaminophen dosing in adults and adolescents weighing 50kg and above.

The maximum daily dose of acetaminophen is based on all routes of administration (i.e., intravenous, oral, and rectal) and all products containing acetaminophen.

Dosing recommendations for different age groups are summarized in Table 1.

**Table 1: Dosing Recommendations**

| Patient Age/Weight | Dose given every 4 hours | Dose given every 6 hours | Maximum total daily dose of acetaminophen (by any routes) |
|---|---|---|---|
| Children, 2 to 12 years of age | 12.5 mg/kg | 15 mg/kg | 75 mg/kg in 24 hours |
| Adults and adolescents ≤ 50 kg | 12.5 mg/kg | 15 mg/kg | 75 mg/kg (up to 3750 mg) in 24 hours |
| Adults and adolescents weighing ≥ 50 kg and no additional factor for hepatotoxicity | 650 mg | 1000 mg | 4000 mg in 24 hours |

### Pediatrics (< 2 years of age)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ACETAMINOPHEN INJECTION in pediatric patients < 2 years of age has not been established; therefore, Health Canada has not authorized an indication for this age group (see 1 INDICATIONS).

### Geriatrics

No dosage adjustments are required. However, as with other drugs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function (see 7 WARNINGS AND PRECAUTIONS and 7.1.4 Geriatrics).

### Hepatic Impairment

In patients with impaired hepatic function or additional risk factors for hepatotoxicity, longer dosing intervals and/or a reduced total daily dose of acetaminophen (3000 mg in 24 hours) may be warranted (see Hepatic/Biliary/Pancreatic).

### Renal Impairment

In patients with severe renal impairment (creatinine clearance ≤ 30 mL/min), it is recommended to reduce the total daily dose and/or increase the minimum interval between each administration to 6 hours (see Renal and Renal Insufficiency).

## 4.4 Administration

- ACETAMINOPHEN INJECTION may be administered without further dilution.
- Use aseptic technique when preparing ACETAMINOPHEN INJECTION.
- Do not add other medications to the ACETAMINOPHEN INJECTION bottle or infusion device.
- Before use, perform the following checks: Read the label. Ensure solution is the one ordered and is within the expiration date.
- Examine the container contents before dose preparation or administering. DO NOT USE if particulate matter, cloudiness or a change in color of solution is observed. The solution is clear and colorless to slightly pinkish-orangish.
- Check the container for leakage or damage. Any container which is suspect should not be used.
- The volume to be administered must not exceed the determined dose. If the entire bottle is not required, using aseptic technique, withdraw the appropriate weight-based dose from an intact ampoule or bottle and place the measured dose in a separate empty, sterile container (e.g. glass bottle, plastic intravenous container, or syringe) for intravenous infusion to avoid the inadvertent delivery and administration of the total volume of the commercially available container.

- Administer the contents of the container intravenously over 15-minutes.
- As with all infusions from a rigid container, monitor the end of the infusion to ensure that air does not enter the system at the end of the infusion.
- ACETAMINOPHEN INJECTION is for single-use only. Discard the unused portion.

**Instructions for Intravenous Administration of Doses Not Equivalent to 500 mg or 1,000 mg**

Doses that are not equivalent to 500 mg or 1,000 mg require aseptic transfer to a separate container prior to dispensing. Discard unused portion. Using aseptic technique, withdraw the appropriate weight-based dose from an intact sealed container and place the measured dose in a separate empty, sterile container (e.g. glass bottle, plastic intravenous container, or syringe) for intravenous infusion to avoid the inadvertent delivery and administration of the total volume of the commercially available container.

Place small volume pediatric doses up to 60 mL in volume in a syringe and administer over 15 minutes using a syringe pump.

**Compatible and Incompatible Solutions**

Table 2 lists commonly administered supportive care drugs and intravenous infusion solutions that are physically compatible for up to four hours at room temperature with ACETAMINOPHEN INJECTION and can therefore be administered in the same IV line.

Diazepam and chlorpromazine hydrochloride are physically incompatible with ACETAMINOPHEN INJECTION in solution and should not be simultaneously administered in intravenous solution.

**Table 2: Intravenous Infusion Solutions Compatible with ACETAMINOPHEN INJECTION**

| Infusion Solution |
|---|
| • 5% dextrose injection<br>• 0.9% sodium chloride injection |

## 4.5 Missed Dose

If a dose is missed, the dose should be administered as soon as it is recognized. If it is almost time for the next dose, skip the missed dose and continue with the next scheduled dose.

# 5 OVERDOSAGE

There is a risk of liver injury (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcohol dependence, in patients with chronic malnutrition and in patients receiving enzyme inducers. Overdosing may be fatal in these cases. Doses higher than those recommended entail the risk of very serious liver damage. Clinical signs and symptoms of liver damage are usually first seen after two days of drug administration with a peak seen, usually after 4–6 days.

**Signs and Symptoms**

In acute acetaminophen overdosage, dose-dependent potentially fatal hepatic necrosis is the most

serious adverse event. Renal tubular necrosis, metabolic acidosis, encephalopathy, hypoglycemic coma, and thrombocytopenia may also occur. Plasma acetaminophen levels > 300 mcg/mL at 4 hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 mcg/mL or < 37.5 mcg/mL at 12 hours after ingestion. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

**Treatment**

Acetylcysteine (chemical name N-acetyl-L-cysteine or NAC) is the antidote for acetaminophen. If an acetaminophen overdose is evident, administer the entire course of NAC treatment as early as possible. If an acetaminophen overdose is suspected, obtain a serum acetaminophen assay at approximately 4 hours following acetaminophen administration. Obtain liver function studies initially and repeat at 24-hour intervals. As a guide to the treatment of overdose, the acetaminophen level can be plotted against time on a nomogram (Rumack-Matthew) which can be used to predict acetaminophen toxicity, and therefore the need for NAC treatment. The lower toxic line on the nomogram is equivalent to 150 mcg/mL at 4 hours and 37.5 mcg/mL at 12 hours. If serum level is above the lower line, administer the entire course of NAC treatment. Withhold NAC therapy if the acetaminophen level is below the lower line.

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 3: Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength | Nonmedicinal Ingredients |
|---|---|---|
| Intravenous | Sterile Solution for Infusion/ 10 mg/mL (available as 100 mg/ 10 mL, 500 mg/ 50 mL and 1000 mg/ 100 mL | glacial acetic acid, mannitol, sodium citrate, water for injection |

ACETAMINOPHEN INJECTION is a sterile, clear, colourless to slightly pinkish-orangish, preservative free, isotonic formulation of acetaminophen intended for intravenous infusion. It has a pH of approximately 5.5.

ACETAMINOPHEN INJECTION is available in cartons of 10 bottles of low-density polyethylene of 100 mL or 50 mL. Acetaminophen Injection is also available in cartons of 20 ampoules of low-density polyethylene of 10 mL.

## 7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

### Cardiovascular

Use caution when administering acetaminophen in patients with severe hypovolemia (e.g., due to dehydration or blood loss).

### Hepatic/Biliary/Pancreatic

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death (see 5 OVERDOSAGE). The maximum daily dose of acetaminophen includes all routes of administration (intravenous, oral and rectal) and all products containing acetaminophen (oral solutions/drops, syrup, pills, capsules, suppositories, combination products, etc.). Do not exceed the maximum recommended daily dose of acetaminophen (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 4 DOSAGE AND ADMINISTRATION).

Acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease. Use caution when administering acetaminophen in patients with mild to moderate hepatic impairment or active hepatic disease, alcohol dependence, or chronic malnutrition (low reserves of hepatic glutathione). Acetylcysteine (chemical name N-acetyl-L-cysteine or NAC), the antidote for acetaminophen, may be considered in cases of overdose (see 5 OVERDOSAGE).

### Hematologic

Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of acetaminophen injection in patients on warfarin, more frequent assessment of INR may be appropriate.

Single doses of acetaminophen injection up to 3000 mg and repeated doses of 1000 mg every 6 hours for 48 hours have not been shown to cause a significant effect on platelet aggregation. Acetaminophen does not have any immediate or delayed effects on small-vessel hemostasis. Clinical studies on both healthy subjects and patients with hemophilia showed no significant changes in bleeding time after receiving multiple doses of oral acetaminophen.

### Immune

There have been post marketing reports of hypersensitivity and anaphylaxis associated with the use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, and pruritus. There were infrequent reports of life-threatening anaphylaxis requiring emergent medical attention. ACETAMINOPHEN INJECTION should be immediately discontinued if symptoms associated with allergy or hypersensitivity occur (see 2 CONTRAINDICATIONS).

### Renal

Use caution when administering acetaminophen in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min). Longer dosing intervals and/or a reduced total daily dose of acetaminophen may be warranted (see 4 DOSAGE AND ADMINISTRATION).

### Skin

Rarely, acetaminophen can cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which

can be fatal. It is important to recognize and react quickly to the initial symptoms of these reactions which may occur without warning but may be manifested by any serious skin reactions.

Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at their first appearance.

## 7.1 Special Populations

### 7.1.1 Pregnant Women

There are no studies of intravenous acetaminophen in pregnant women and it is therefore not known whether ACETAMINOPHEN INJECTION can cause fetal harm when administered to a pregnant woman. However, data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations or fetotoxic effects.

ACETAMINOPHEN INJECTION should be given to a pregnant woman only if the benefit to the mother clearly outweighs the risk to the fetus. If clinically needed, acetaminophen can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

### 7.1.2 Breast-feeding

While dedicated studies with acetaminophen injection in nursing women have not been conducted, acetaminophen is secreted in human milk after oral administration. Based on data from 32 nursing mothers, less than 2% of the weight-based dose given orally to the mother transfers through breast milk to the nursing child. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use. The benefits of breast feeding while on ACETAMINOPHEN INJECTION should therefore be weighed against the risks to the infant.

### 7.1.3 Pediatrics

In pediatric patients younger than 2 years of age, the safety and efficacy of ACETAMINOPHEN INJECTION for the treatment of acute pain and fever have not been established. ACETAMINOPHEN INJECTION is not recommended for this age group (see 1.1 Pediatrics). The presence of hyperbilirubinemia is associated with acetaminophen clearance reduction in neonates (see 10.3 Pharmacokinetics).

In pediatric patients 2 years of age and older, the safety and efficacy of ACETAMINOPHEN INJECTION for the treatment of acute pain and fever are supported by evidence from adequate and well-controlled studies of acetaminophen injection in adults and from pharmacokinetic and controlled studies in pediatrics (see 10.3 Pharmacokinetics and 14 CLINICAL TRIALS).

### 7.1.4 Geriatrics

Of the total number of subjects in clinical studies with acetaminophen injection, 16% percent were aged 65 and over. No overall differences in safety or efficacy were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. As with other drugs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function (see Cardiovascular; Hepatic/Biliary/Pancreatic and Renal).

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

A total of 1020 adult patients have received acetaminophen injection in clinical trials, including 37.3% (n = 380) who received 5 or more doses, and 17.0% (n = 173) who received more than 10 doses. Most patients were treated with acetaminophen injection 1000 mg every 6 hours following surgery. A total of 13.1% (n = 134) received acetaminophen injection 650 mg every 4 hours. Approximately 69% of acetaminophen -treated and 71% of placebo-treated patients experienced adverse events (AEs). These AEs were predominantly of mild and moderate severity. The most common adverse events (incidence ≥ 5%) in adult patients treated with acetaminophen injection were nausea, vomiting, headache, and insomnia.

A total of 355 pediatric patients (47 neonates, 64 infants, 171 children, and 73 adolescents) have received acetaminophen injection in active-controlled (n = 250) and open-label clinical trials (n = 225), including 59.7% (n = 212) who received 5 or more doses and 43.1% (n = 153) who received more than 10 doses. Pediatric patients received acetaminophen injection doses up to 15 mg/kg on an every 4 hour, every 6 hour, or every 8 hour schedule. The maximum exposure was 7.7, 6.4, 6.8, and 7.1 days in neonates, infants, children, and adolescents, respectively. Approximately 48% of acetaminophen injection-treated patients experienced adverse events which were predominantly of mild and moderate severity. The most common adverse events (incidence ≥ 5%) in pediatric patients treated with acetaminophen injection were nausea, vomiting, constipation, pruritus, agitation, and atelectasis.

### 8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Treatment-emergent adverse events (TEAEs) reported in ≥ 1% of acetaminophen injection-treated post-operative adult patients in placebo-controlled, repeat-dose clinical trials are summarized in Table 4 if they occurred at a numerically higher rate with acetaminophen injection than with placebo. These adverse events were included regardless of any causal relationship to acetaminophen injection.

**Table 4: Treatment-Emergent Adverse Events in Placebo-Controlled, Repeat Dose Clinical Studies Reported by ≥ 1% of Acetaminophen Injection-Treated Adult Patients and at a Numerically Higher Frequency than Placebo**

| System Organ Class – Preferred Term | Acetaminophen (N = 402) n (%) | Placebo (N = 379) n (%) |
|---|---|---|
| **Gastrointestinal Disorders** | | |
| Nausea | 138 (34.3) | 119 (31.4) |
| Vomiting | 62 (15.4) | 42 (11.1) |
| Abdominal distention | 18 (4.5) | 14 (3.7) |
| Abdominal pain | 10 (2.5) | 7 (1.8) |
| Dyspepsia | 8 (2.0) | 6 (1.6) |
| **General Disorders and Administration Site Conditions** | | |
| Injection site extravasation | 11 (2.7) | 9 (2.4) |
| Infusion site pain | 9 (2.2) | 4 (1.1) |
| Peripheral edema | 5 (1.2) | 3 (0.8) |
| Chills | 5 (1.2) | 1 (0.3) |
| **Injury, Poisoning, and Procedural Complications** | | |
| Incision site pain | 7 (1.7) | 1 (0.3) |
| **Investigations** | | |
| Increased Aspartate aminotransferase (AST) | 6 (1.5) | 3 (0.8) |
| Increased Gamma-glutamyl transferase (GGT) | 5 (1.2) | 1 (0.3) |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Muscle spasms | 6 (1.5) | 5 (1.3) |
| Pain in extremity | 5 (1.2) | 3 (0.8) |
| **Nervous System Disorders** | | |
| Headache | 39 (9.7) | 33 (8.7) |
| **Psychiatric Disorders** | | |
| Insomnia | 30 (7.5) | 21 (5.5) |
| **Renal and Urinary Disorders** | | |
| Dysuria | 8 (2.0) | 7 (1.8) |
| **Vascular Disorders** | | |
| Hypotension | 7 (1.7) | 1 (0.3) |

These spontaneously reported TEAEs in adults, particularly the frequent gastrointestinal TEAEs such as nausea and vomiting, should be considered in the context of the patient population (post-operative patients) where numerous adverse events are expected.

### 8.2.1 Clinical Trail Adverse Reaction - Pediatrics

Treatment-emergent adverse events reported in ≥ 1% of acetaminophen injection-treated post-operative hospitalized pediatric patients with pain or fever (n = 355) in active and/or open-label

studies are summarized below. These adverse events were included regardless of any causal relationship to acetaminophen injection.

- **Blood and lymphatic system disorders:** anemia (3.1%)
- **Cardiac disorders:** tachycardia (1.1%)
- **Gastrointestinal disorders:** nausea (15.2%), vomiting (10.4%), constipation (8.2%), diarrhea (2.3%), abdominal pain (1.1%)
- **General disorders and administration site conditions:** pyrexia (4.2%), injection site pain (3.4%), peripheral edema (1.1%)
- **Infections and infestations:** wound infection (1.1%)
- **Investigations:** increased hepatic enzyme (1.1%)
- **Metabolism and nutrition disorders:** hypokalemia (3.9%), hypomagnesemia (3.9%), hypoalbuminemia (1.7%), hypophosphatemia (1.4%), hypervolemia (1.1%)
- **Musculoskeletal and connective tissue disorders:** muscle spasm (2.0%), pain in extremity (1.1%)
- **Nervous system disorders:** headache (2.5%)
- **Psychiatric disorders:** agitation (5.6%), insomnia (1.1%)
- **Renal and urinary disorders:** oliguria (1.4%)
- **Respiratory, thoracic and mediastinal disorders:** atelectasis (5.4%), pleural effusion (3.7%), pulmonary edema (2.5%), wheezing (2.3%), stridor (2.0%), hypoxia (1.1%)
- **Skin and subcutaneous tissue disorders:** pruritus (7.9%), periorbital edema (1.1%), rash (1.1%)
- **Vascular disorders:** hypotension (2.5%), hypertension (1.1%)

### 8.3 Less Common Clinical Trial Adverse Reactions

The following TEAEs, which have been included regardless of any causal relationship to acetaminophen, were reported by adult subjects treated with acetaminophen injection in placebo-controlled clinical studies (n = 402) and occurred with an incidence of > 0.3% to < 1% and were observed at a numerically higher incidence with acetaminophen injection than with placebo (n = 379).

- **Cardiac disorders:** palpitations
- **Gastrointestinal disorders:** gastroesophageal reflux disease, abnormal bowel sounds, abdominal tenderness, hemorrhoids, rectal spasm, small intestinal obstruction
- **General disorders and administration site conditions:** injection site pain
- **Infections and infestations:** pneumonia, wound infection, vulvovaginal mycotic infection
- **Injury, poisoning and procedural complications:** incision site hemorrhage, seroma
- **Investigations:** increased alanine aminotransferase (ALT), decreased blood magnesium, decreased blood potassium
- **Metabolism and nutrition disorders:** hypoglycemia
- **Renal and urinary disorders:** pollakiuria

- **Respiratory, thoracic, and mediastinal disorders:** dyspnea, cough, productive cough
- **Skin and subcutaneous tissue disorders:** erythema, night sweats
- **Vascular disorders:** hypertension

### 8.3.1 Less Common Clinical Trial Adverse Drug Reactions - Pediatrics

The following TEAEs, which have been included regardless of any causal relationship to acetaminophen, occurred with an incidence of > 0.3% to < 1% among acetaminophen injection-treated pediatric patients in active and open-label clinical studies:

- **Blood and lymphatic system disorders:** thrombocytopenia
- **Eye disorders:** dry eye
- **Gastrointestinal disorders:** abdominal distension, upper abdominal pain
- **General disorders and administration site conditions:** catheter related complication, catheter site discharge, face edema, generalized edema, injection site extravasation, edema
- **Hepatobiliary disorders:** hepatotoxicity
- **Infections and infestations:** abdominal abscess, incision site infection, laryngotracheitis, upper respiratory tract infection
- **Investigations:** decreased hemoglobin, decreased oxygen saturation, increased platelet count
- **Metabolism and nutrition disorders:** hypocalcemia
- **Musculoskeletal and connective tissue disorders:** back pain, muscular weakness
- **Nervous system disorders:** brain edema, burning sensation, dizziness
- **Psychiatric disorders:** anxiety, depression
- **Renal and urinary disorders:** polyuria
- **Respiratory, thoracic and mediastinal disorders:** chylothorax, obstructive airways disorder, pharyngolaryngeal pain, respiratory failure
- **Skin and subcutaneous tissue disorders:** blister, skin disorder

## 8.5 Post-Market Adverse Reactions

Because post-market adverse events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse events have been reported:

Acute hepatitis, hepatic failure, hepatitis fulminant, anaphylactic shock, anaphylactic/anaphylactoid reactions, hypotension, angioedema, urticaria, cardiac arrest, acute renal failure, bronchospasm, respiratory distress, agranulocytosis, neutropenia, thrombocytopenia, and leucopenia.

In patients with G-6-PD (glucose-6-phosphate dehydrogenase) deficiency conflicting reports have suggested a possible association with hemolytic anemia.

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

Acetaminophen is metabolized by the liver via three major pathways: glucuronidation, sulfation, and oxidation.

Acetaminophen, regardless of route of administration, appears to have only limited potential for drug-drug interactions. The drug interactions described below are those which have been generally reported with oral acetaminophen.

### 9.3 Drug-Behavioural Interactions

The effects of alcohol are complex, because excessive alcohol usage can induce hepatic cytochromes, but alcohol also acts as a competitive inhibitor of the metabolism of acetaminophen. Because chronic, excessive consumption of alcohol may increase the risk of acetaminophen-induced hepatotoxicity, patients with alcohol dependence should be cautioned to avoid regular or excessive use of acetaminophen, or alternatively, to avoid chronic ingestion of alcohol.

### 9.4 Drug-Drug Interactions

Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. The clinical consequences of these effects have not been established.

Caution is advised when concomitant intake of enzyme-inducing drugs is considered. These drugs include, but are not limited to, barbiturates; isoniazid; zidovudine; and carbamazepine.

Probenecid causes an almost 2-fold reduction in clearance of acetaminophen by inhibiting its conjugation with glucuronic acid. A reduction of the acetaminophen dose should be considered for concomitant treatment with probenecid.

Salicylamide may prolong the elimination half-life of acetaminophen.

Concomitant administration of diflunisal and acetaminophen to normal volunteers resulted in significantly increased (50%) plasma levels of acetaminophen. Acetaminophen had no effect on plasma levels of diflunisal. Caution is advised when diflunisal and higher doses of acetaminophen are co-administered.

Tyrosine kinase inhibitors imatinib and sorafenib inhibit acetaminophen glucuronidation in vitro. However, a clinical effect was not shown in any studies. Systemic exposure to acetaminophen may be increased when co-administered with these drugs. Caution is recommended in patients with hepatic impairment or at risk of hepatotoxicity.

Busulfan is eliminated from the body via conjugation with glutathione. Concomitant use with acetaminophen may result in reduced busulfan clearance.

**Anticoagulants**
Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in International normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of acetaminophen in patients on warfarin, more frequent assessment of INR may be

appropriate in such circumstances.

### 9.5 Drug-Food Interactions

As an intravenous medication, studies evaluating interactions with food are not relevant.

Hepatotoxicity has been reported in fasting patients ingesting 4 to 10 g of acetaminophen. Caution should be used when administering ACETAMINOPHEN INJECTION to patients presenting with severe or chronic malnutrition.

### 9.6 Drug-Herb Interactions

As an intravenous medication, studies evaluating interactions with herbs are not relevant.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Acetaminophen is a centrally acting analgesic and antipyretic agent. Although the exact site and mechanism of action of acetaminophen are not clearly defined, its effectiveness as an antipyretic agent has been attributed to its effect on the hypothalamic heat-regulating center, while its analgesic effect is due to raising the pain threshold. Potential mechanisms of action include central effects upon prostaglandin synthesis, the cannabinoid receptor system, the serotonergic system, and the neurons expressing receptors for transient receptor potential ankyrin-1 (TRPA1) and vanilloid-1 (TRPV1). There are no reliable pharmacodynamic markers of activity. Peripheral actions appear to be minimal.

### 10.2 Pharmacodynamics

Acetaminophen has been shown to have analgesic and antipyretic activities in animal and human studies. IV acetaminophen was equally or more potent than oral or intraperitoneal administered acetaminophen, as demonstrated by its activity in the mouse writhing test.

### 10.3 Pharmacokinetics

The pharmacokinetics of acetaminophen injection have been studied in patients and healthy subjects from premature neonates up to adults 60 years old. As shown in Table 5, the pharmacokinetic profile of acetaminophen injection in children and adolescents is comparable to that in adults, but the pharmacokinetic exposure is higher in neonates and infants (0-2 years of age). The presence of hyperbilirubinemia is associated with acetaminophen clearance reduction in neonates. In addition, the presence of hyperbilirubinemia is associated with acetaminophen clearance reduction in neonates.

#### Absorption

The pharmacokinetic profile of acetaminophen injection has been demonstrated to be dose proportional in adults following administration of single 500, 650 and 1000 mg doses.

The maximum concentration (Cmax) of acetaminophen in plasma occurs at the end of the 15 minute intravenous infusion of acetaminophen. Compared to the same dose of oral acetaminophen elixir, the plasma Cmax following administration of acetaminophen injection is up to 70% higher and the Tmax

approximately 30 minutes sooner (45 minutes sooner compared to caplets), while overall systemic exposure (area under the concentration-time curve [AUC]) is very similar.

The pharmacokinetic parameters of acetaminophen injection (pharmacokinetic exposure [AUC0-τ, Cmax, terminal elimination half-life [T½], systemic clearance [CL], and volume of distribution at steady state [Vss]) following administration of a single intravenous dose of 15 mg/kg for the pediatric population and 1000 mg in adults are summarized in Table 5. The AUC0-τ observed in children and adolescents is similar to adults, but higher in neonates and infants (see Table 5).

**Table 5: Summary of Acetaminophen Injection Pharmacokinetic Parameters[a]**

| Subpopulations | Mean (SD) | | | | |
|---|---|---|---|---|---|
| | $AUC_{0-\tau}$[b] (µg × h/mL) | Cmax (µg/mL) | T½ (h) | CL (L/h/kg) | Vss[c] (L/kg) |
| Neonates (≤ 28 days old) | 62 (11) | 25 (4) | 7.0 (2.7) | 0.12 (0.04) | 1.1 (0.2) |
| Infants (29 days to < 2 years old) | 57 (54) | 29 (24) | 4.2 ( 2.9) | 0.29 (0.15) | 1.1 (0.3) |
| Children (2 years to < 12 years old) | 38 (8) | 29 (7) | 3.0 (1.5) | 0.34 (0.10) | 1.2 (0.3) |
| Adolescents (12 years to ≤ 16 years old) | 41 (7) | 31 (9) | 2.9 (0.7) | 0.29 (0.08) | 1.1 (0.3) |
| Adults ( > 16 years old) | 43 (11) | 28 (21) | 2.4 (0.6) | 0.27 (0.08) | 0.8 (0.2) |

[a] Single dose mean
[b] $AUC_{0-\tau}$ was calculated after the first dose from 0 to 8 hours for neonates and 0 to 6 hours for infants, children, adolescents, and adults;
[c] Vss (Volume of distribution at steady sate) determined using non-compartmental method

Dosing simulations from pharmacokinetic data in infants and neonates suggest that dose reductions of 33% in infants 1 month to < 2 years of age, and 50% in neonates up to 28 days, with a minimum dosing interval of 6 hours, will produce a pharmacokinetic exposure similar to that observed in children age 2 years and older.

### Distribution

At therapeutic levels, binding of acetaminophen to plasma proteins is low (ranging from 10% to 25%). Acetaminophen appears to be widely distributed throughout most body tissues except fat.

### Metabolism

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: conjugation with glucuronide, conjugation with sulfate, and oxidation via the cytochrome P450 enzyme pathway, primarily CYP2E1, to form a reactive intermediate metabolite (N-acetyl-p-benzoquinone imine or NAPQI). With therapeutic doses, NAPQI undergoes rapid conjugation (and deactivation) with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates which are excreted in the urine.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide- and sulfate-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

### Elimination

Acetaminophen metabolites are mainly excreted in the urine. Less than 5% is excreted in the urine as unconjugated (free) acetaminophen in adults and more than 90% of the administered dose is excreted within 24 hours.

### Special Populations and Conditions

- **Renal Insufficiency**

In cases of severe renal impairment (creatinine clearance 10-30 mL/min), the elimination of acetaminophen is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min), the minimum interval between each administration should be increased to 6 hours (see Renal Impairment).

## 11 STORAGE, STABILITY AND DISPOSAL

ACETAMINOPHEN INJECTION should be stored at 15 °C to 25 °C: do not refrigerate or freeze. ACETAMINOPHEN INJECTION is for single use only. Use immediately upon opening: discard unused portion. Keep the container in the outer carton in order to protect from light.

## PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

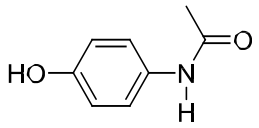
### Drug Substance

Proper name: acetaminophen

Chemical name: *N*-acetyl-p-aminophenol

Molecular formula and weight: $C_8H_9NO_2$ and 151.16

Structural formula:




Physicochemical properties: Acetaminophen occurs as a white, odorless powder with a melting point between 168-172 ºC.

## 14 CLINICAL TRIALS

### 14.1 Clinical Trials by Indication

### Indication for Pain

**Table 6: Summary of Patient Demographics in Clinical Trials for Treatment of Pain**

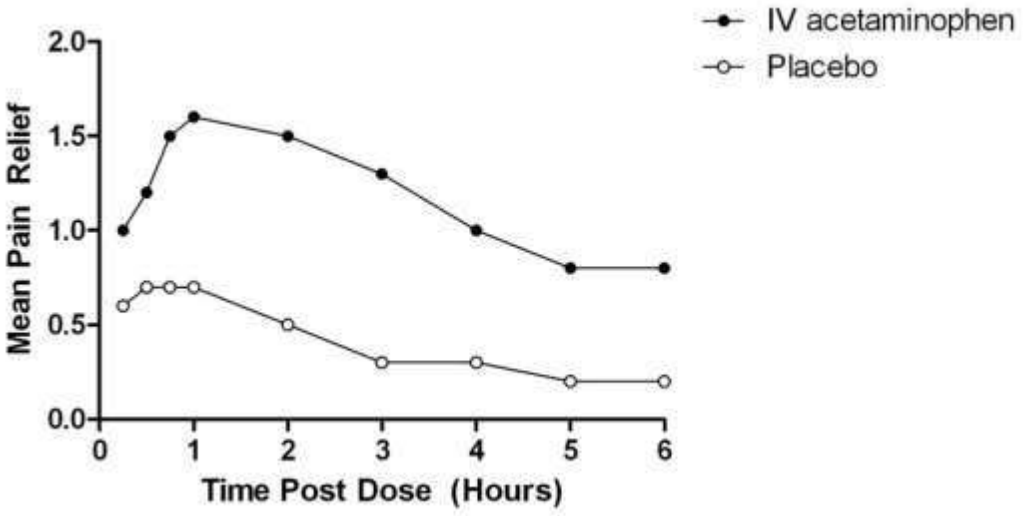
| Study # | Study Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean age (Range) | Sex % |
|---|---|---|---|---|---|
| **Study 1**<br>Postoperative pain following total hip or knee replacement | Randomized, double-blind, 3-parallel-group, active- and placebo-controlled | 4 doses q6h over 24 hours.<br>Treatment Groups:<br>1 g IV acetaminophen, 2 g IV propacetamol, or IV placebo | n = 151 | 60.1 years (22 – 87) | M: 51%<br>F: 49% |
| **Study 2**<br>Postoperative pain following abdominal laparoscopic surgery | Randomized, double-blind, placebo-controlled with optional open-label extension up to 5 days | 4 doses q6h (1 g IV acetaminophen or placebo) or 6 doses q4h (650 mg IV acetaminophen or placebo) over 24 hours | n = 244 | 46.2 years (18 – 78) | M: 19%<br>F: 81% |

**Study 1**

Study 1 was a phase III, randomized, double-blind, placebo-controlled study which assessed the analgesic efficacy and safety of single and repeated doses (q6h for 24 hours) of acetaminophen injection 1000 mg for the treatment of postoperative pain in 101 patients with moderate to severe pain following total hip or knee replacement. Throughout the study, subjects had access to rescue medication (morphine) at all times to treat pain.

Following a single dose, a statistically significant difference favoring acetaminophen injection compared to placebo was observed for pain relief (PR) at 15 minutes ($p = 0.017$, Figure 1). Key secondary efficacy endpoints related to PR and pain intensity (PI) in single and repeated doses were also supportive in favor of acetaminophen injection.

**Figure 1: Protocol-defined Primary Efficacy Analysis: Mean Pain Relief**




**Study 2**

Study 2 was a phase III, randomized, double-blind, placebo-controlled, multi-center, parallel-group, repeated-dose study which assessed the analgesic efficacy and safety of acetaminophen injection 1000 mg q6h, or 650 mg q4h, for 24 hours versus placebo in the treatment of 200 patients with moderate to severe postoperative pain after abdominal laparoscopic surgery. Throughout the study, subjects had access to rescue medication (various opioids) at all times to treat pain.

A statistically significant difference of $p = 0.0068$ (1000 mg group) and $p = 0.0183$ (650 mg group) favoring acetaminophen injection compared to placebo was observed for the sum of PI differences over 24 hours (SPID24). The key secondary efficacy endpoints were also statistically significant in favor supportive of acetaminophen injection over placebo.

**Indication for Fever**

**Table 7: Summary of Patient Demographics for Clinical Trials in Treatment of Fever**

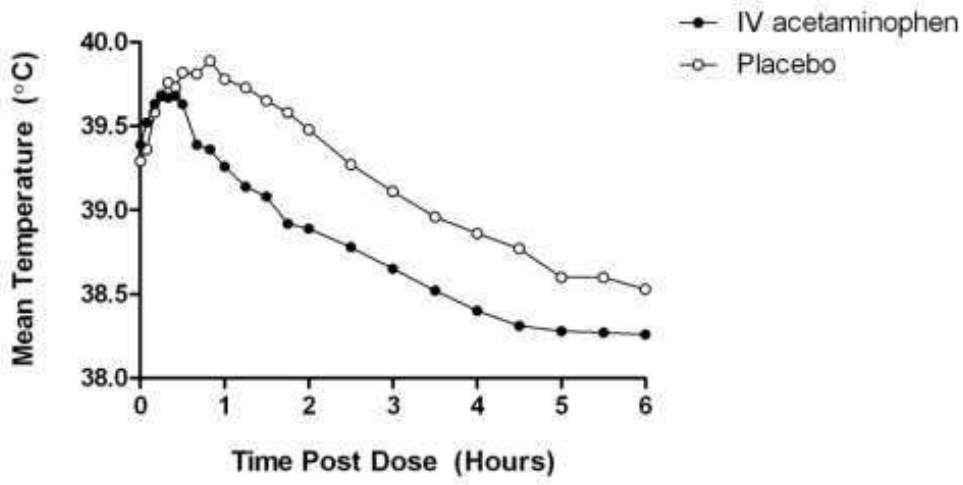
| Study | Study Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean age (Range) | Sex % |
|---|---|---|---|---|---|
| **Study 3** Antipyretic in an endotoxin-induced fever model | Randomized, double-blind, parallel-group, placebo-controlled | 1 dose of 1 g IV acetaminophen or placebo | n = 60 | 29.9 years (18 – 55) | M: 100% F: 0% |

**Study 3**

Study 3 was a phase III, randomized, double-blind, placebo-controlled, single-dose study to assess the antipyretic efficacy and safety of acetaminophen injection versus placebo for the treatment of endotoxin-induced fever in 60 healthy adult males over 6 hours.

A statistically significant antipyretic effect of acetaminophen injection was observed compared to placebo (p = 0.0001) by measurement of the weighted sum of the temperature differences through 6 hours (WSTD6). Treatment with acetaminophen injection reduced the peak temperature compared to placebo, and caused a more rapid decline in temperature (Figure 2).

**Figure 2: Mean Temperature (°C) Over Time**




**Adult Fever (Supportive Study 4)**

A supportive single-dose, endotoxin-induced, fever study was conducted in 81 healthy adult males to compare efficacy of acetaminophen injection versus oral acetaminophen. Fever reduction and time to

onset of action were the key efficacy variables for the study. Acetaminophen injection was more efficacious than oral acetaminophen in reducing fever within 2 hours after administration and demonstrated a more rapid onset of action compared to oral acetaminophen at 30 minutes.

### Pediatric Acute Pain and Fever

Acetaminophen injection was studied in 355 patients across the full pediatric age strata, from premature neonates (≥ 32 weeks post menstrual age) to adolescents, in two active-controlled and three open-label safety and pharmacokinetic trials.

In pediatrics older than 2 years of age, the safety and efficacy results of the studies for the treatment of acute pain and fever suggest that acetaminophen can be used in this age group. This is also supported by the similarity of the PK profile of children, adolescents, and adults (see Table 5).

In pediatric patients younger than 2 years of age, the efficacy for the treatment of acute pain and fever has not been established.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product. Acetaminophen Injection is not an antimicrobial drug.

## 16 NON-CLINICAL TOXICOLOGY

### Overview

The toxicity associated with acetaminophen is dose-dependent with a threshold effect. The main target organ is the liver. Toxicity usually results from much higher than therapeutic doses and depends on the formation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). This metabolite is formed by cytochrome P450 (CYP450) isoforms, particularly CYP2E1 in most species including humans. With therapeutic dosing, NAPQI reacts rapidly with the reduced form of glutathione to produce non-toxic conjugates that are then excreted by the kidneys. The detoxification reaction requires hepatic reduced form of glutathione. With toxic doses of acetaminophen, physiological glutathione concentration is not sufficient, allowing NAPQI to react covalently with essential hepatic proteins and other macromolecules. Subsequent damage to mitochondria, cell membranes, and nuclei, as well as the disruption of cell death- and survival-related signaling pathways, leads to apoptosis and/or necrosis.

### General Toxicology

IV acetaminophen was evaluated in repeat-dose toxicity studies in rats up to 28 days. IV formulations of acetaminophen were well tolerated systemically, with all adverse events being attributed to the infusion system or to the high volumes infused.

### Carcinogenicity

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the MHDD of 4 grams/day, based on a body surface area comparison. In

contrast, there was no evidence of carcinogenic activity in male rats (0.7 times) or mice (1.2-1.4 times the MHDD, based on a body surface area comparison).

**Genotoxicity**

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive in the in vitro mouse lymphoma assay and the in vitro chromosomal aberration assay using human lymphocytes. In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

**Reproductive and Developmental Toxicology**

- **Impairment of Fertility**

In studies conducted by the US National Toxicology Program, fertility assessments have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison.

Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHDD (based on a body surface area comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

- **Development Studies**

While animal reproduction studies have not been conducted with intravenous acetaminophen, studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times the maximum human daily dose (MHDD = 4 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations.

When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3-times the MHDD, based on a body surface area comparison.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at

all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

**Special Toxicology**

- **Local Tolerance Studies**

Nonclinical studies showed that acetaminophen infusions were well tolerated locally in rabbits and that acetaminophen did not cause hypersensitivity reactions in the guinea pig.

- **Dependence and Tolerance**

Acetaminophen injection did not cause any opiate-like withdrawal symptoms in mice.

**PATIENT MEDICATION INFORMATION**

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PrACETAMINOPHEN INJECTION**

**Acetaminophen Injection**

Read this carefully before you are given **ACETAMINOPHEN INJECTION**. 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 **ACETAMINOPHEN INJECTION**.

**Serious Warnings and Precautions**

**Acetaminophen Limits:** If you take other medicines that may contain acetaminophen, tell your healthcare professional before ACETAMINOPHEN INJECTION is given to you as this will help them determine the right dose for you.

Acetaminophen can be found in:

- oral solutions / drops,
- syrups,
- pills,
- capsules,
- suppositories,
- intravenous solutions, etc.

Read the labels on all products you take to see if they contain acetaminophen:

- Use the labels to calculate how much acetaminophen you have had in a day.
- Keep track of how much acetaminophen is in each dose and how much you have taken in 24 hours.

**Liver Problems:** Treatment with ACETAMINOPHEN INJECTION can cause liver damage and failure. This can lead to serious complications or even death. This may be more likely to happen if the amount of acetaminophen exceeds the maximum daily limits. Your healthcare professional will prepare and give you ACETAMINOPHEN INJECTION. Your dose may depend on your condition, weight, and if you are taking other medicines that contain acetaminophen.

See the **Serious side effects and what to do about them** table, below, for more information on this and other serious side effects.

**What is ACETAMINOPHEN INJECTION used for?**

ACETAMINOPHEN INJECTION is used in adults and children (2 years of age and older) to manage and treat short term:

- mild to moderate pain;
- moderate to severe pain when given with medicines known as opioids; and
- fevers.

ACETAMINOPHEN INJECTION should be given when it is necessary to give acetaminophen through a vein ("intravenously" or "IV").

**How does ACETAMINOPHEN INJECTION work?**

ACETAMINOPHEN INJECTION belongs to a group of medicines known as analgesics (pain relievers) and antipyretics (fever reducer). The way ACETAMINOPHEN INJECTION works is not known. However, it is thought to work by blocking chemical messengers in the brain that cause pain and fever.

**What are the ingredients in ACETAMINOPHEN INJECTION?**

Medicinal ingredient: acetaminophen.

Non-medicinal ingredients: glacial acetic acid, mannitol, sodium citrate and water for injections.

**ACETAMINOPHEN INJECTION comes in the following dosage forms:**

Solution for Infusion: 10 mg/mL of acetaminophen.

**Do not use ACETAMINOPHEN INJECTION if:**

- you are allergic to acetaminophen or to any other ingredients in ACETAMINOPHEN INJECTION;
- you have severe kidney problems;
- you have severe liver problems.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ACETAMINOPHEN INJECTION. Talk about any health conditions or problems you may have, including if you:**

- have taken other medications containing acetaminophen in the past 24 hours;
- have liver problems;
- have kidney problems;
- have alcohol dependence or regularly drink alcohol (three or more drinks per day);
- suffer from malnutrition;
- have low blood or fluids in your body (hypovolemia). This can be happen from dehydration or blood loss;
- are breastfeeding or planning to breastfeed. ACETAMINOPHEN INJECTION can pass into breast milk;
- are pregnant or planning to become pregnant. It is not known if ACETAMINOPHEN INJECTION can cause harm to your unborn baby;
- are 65 years of age or older, especially if you also have kidney, liver, and/or heart problems.
- are taking warfarin (a drug to prevent clotting of blood).

**Other warnings you should know about:**

**ACETAMINOPHEN INJECTION can cause the following:**

- **Allergic reactions:** ACETAMINOPHEN INJECTION can cause an allergic reaction. The symptoms can include swelling of the face, mouth, and throat, breathing problems, hives, rashes, and itchiness. If you notice any symptoms of an allergic reaction, stop taking ACETAMINOPHEN INJECTION right away and tell your healthcare professional.
- **Severe skin reactions:** ACETAMINOPHEN INJECTION can cause severe skin reactions. This can include acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). If you notice any signs of a skin reaction, stop taking ACETAMINOPHEN INJECTION right away and tell your healthcare professional.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

**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 ACETAMINOPHEN INJECTION:**

- alcohol;
- barbiturates, a medicine used to cause a sleeping and calming effect;
- busulfan, a medicine used to treat cancer;

- carbamazepine, a medicine used to treat and manage seizures;
- isoniazid, a medicine used to treat tuberculosis;
- probenecid, a medicine used to treat gout or gouty arthritis;
- zidovudine, a medicine used to prevent and treat HIV;
- medicines used to thin the blood and prevent blood clots (e.g., warfarin);
- medicines used to treat pain and reduce fever (e.g., salicylamide and diflunisal);
- medicines known as tyrosine kinase inhibitors (e.g., imatinib and sorafenib).

**How to take ACETAMINOPHEN INJECTION:**

Your healthcare professional will prepare and give you ACETAMINOPHEN INJECTION. You will receive ACETAMINOPHEN INJECTION through your veins (i.e., "intravenously" or "IV") by slow injection over 15 minutes.

**Usual dose:**

Your healthcare professional will decide the right dose for your treatment and how long you should be treated with ACETAMINOPHEN INJECTION. Your dose may depend on your condition, weight, and if you are taking other medicines that contain acetaminophen.

**Overdose:**

The symptoms of an overdose with ACETAMINOPHEN INJECTION can include:

- kidney problems;
- liver problems;
- encephalopathy (a disease that affects the brain function or structure);
- low blood sugar levels;
- coma;
- low blood platelet levels;
- nausea;
- vomiting;
- excessive or abnormal sweating; or
- not feeling well.

If you think you, or a person you are caring for, have received too much ACETAMINOPHEN INJECTION, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If a dose is missed, the dose should be given to you by your healthcare professional as soon as it is recognized. If it is almost time for the next dose, the missed dose will be skipped and the next scheduled dose will be given.

**What are possible side effects from using ACETAMINOPHEN INJECTION?**

These are not all the possible side effects you may have when taking ACETAMINOPHEN INJECTION. If you experience any side effects not listed here, tell your healthcare professional.

**The side effects in adults include:**

- difficulty sleeping;
- headache;
- nausea;
- vomiting.

**The side effects in children include:**

- agitation;
- constipation;
- itchy skin;
- lung collapse;
- nausea;
- vomiting.

| 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** | |
| **RARE** | | | |
| **Anaphylactic shock** (immediate violent allergic reaction): low blood pressure, hives, itchiness, pale skin, wheezing, difficulty breathing, nausea, vomiting, diarrhea, dizziness, or fainting. | | | √ |
| **Angioedema** (swelling of a tissue such as the lips, eyes, joints). | | √ | |
| **Hypotension** (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up). | | √ | |
| **Neutropenia** (decreased white blood cells): infections, fatigue, fever, aches, pains, or flu-like symptoms. | | √ | |
| **Respiratory distress:** difficulty breathing, bluish colour around the mouth, inside of the lips or on the fingernails, sweating, or wheezing. | | √ | |
| **Thrombocytopenia** (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue, or weakness. | | √ | |
| **Urticaria** (a kind of skin rash, also known as hives). | √ | | |
| **VERY RARE** | | | |
| **Liver problems:** yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, tiredness, fever, or dark urine. | | √ | |

| 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 | |
| **Serious skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis):** any combination of itchy skin rash, redness, blistering and peeling of the skin and/or of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches, joint pain, yellowing of the skin or eyes, dark urine, or swollen glands. | | | √ |
| **UNKNOWN FREQUENCY** | | | |
| **Allergic reaction:** swelling of the face, lip or throat, red and lumpy skin, rash, itchiness, hives, difficulty breathing or swallowing, wheezing feeling sick to your stomach, or vomiting. | | | √ |

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/adverse-reaction-reporting.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 healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

ACETAMINOPHEN INJECTION will be stored by your healthcare professional between 15°C to 25°C. Do not refrigerate or freeze. Keep the container in the outer carton in order to protect from light. Keep out of reach and sight of children.

**If you want more information about ACETAMINOPHEN INJECTION:**

- 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); or by calling 1-800-854-6851.

This leaflet was prepared by B. Braun of Canada Ltd.

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