

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**Pr ACETAMINOPHEN INJECTION**

Acetaminophen Injection

1000 mg/100 mL  
(10 mg/mL)

Sterile solution for intravenous infusion

Analgesic and Antipyretic

ATC Code: N02BE01

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## RECENT MAJOR LABEL CHANGES

Not applicable.

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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

#### Adults

ACETAMINOPHEN INJECTION (acetaminophen injection) is indicated for:

- the short-term management of mild to moderate pain when administration by IV route is deemed clinically necessary
- the management of moderate to severe pain with adjunctive opioid analgesics
- the treatment of fever.

ACETAMINOPHEN INJECTION may be given in single or repeated doses when an intravenous route of administration is considered clinically appropriate.

#### Pediatrics

##### Pediatrics ≥ 2 years of age

ACETAMINOPHEN INJECTION is indicated for:

- the short-term management of mild to moderate pain when administration by IV route is deemed clinically necessary
- the management of moderate to severe pain with adjunctive opioid analgesics
- the treatment of fever

ACETAMINOPHEN INJECTION may be given in single or repeated doses when an intravenous route of administration is considered clinically appropriate.

##### 1.1 Pediatrics (< 2 years of age)

There is limited data on the use of ACETAMINOPHEN INJECTION in pediatric patients less than 2 years of age. ACETAMINOPHEN INJECTION is not recommended for this age group. ACETAMINOPHEN INJECTION contains povidone; there is limited data supporting its safe use in this age group (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

##### 1.2 Geriatrics (> 65 years of age)

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.

### 2 CONTRAINDICATIONS

ACETAMINOPHEN INJECTION is contraindicated in:

- patients who have previously demonstrated hypersensitivity to acetaminophen, to any ingredient in the formulation, or component of the container (see **DOSAGE FORMS, 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 **DOSAGE AND ADMINISTRATION** and **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 INJECTION contains acetaminophen. 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 **OVERDOSAGE** and **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 Dosing Considerations

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**.

- 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.

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 ACETAMINOPHEN INJECTION dosing in adults and adolescents weighing 50 kg 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**

Age group	Dose given every 6 hours	Volume given every 6 hours	Maximum total daily dose of acetaminophen (by any route)
Children, 2 years – 12 years	15 mg/kg	1.5mL solution per kg	75 mg/kg in 24 hours
Adults and adolescents weighing < 50 kg	15 mg/kg	1.5mL solution per kg	75 mg/kg in 24 hours (up to 3750 mg)
Adults and adolescents weighing ≥ 50 kg	1000 mg	one 100mL bag	4000 mg in 24 hours

## 4.3 Administration

For adult and adolescent patients weighing ≥ 50 kg requiring 1000 mg doses of ACETAMINOPHEN INJECTION, administer the dose by inserting an IV set through the septum of the bag. ACETAMINOPHEN INJECTION may be administered without further dilution. The solution is clear and colorless to off-white/yellow. Examine the bag contents before dose preparation or administering. DO NOT USE if particulate matter, cloudiness or a change in color of solution is observed. Administer the contents of the bag intravenously over 15-minutes. Use aseptic technique when preparing ACETAMINOPHEN INJECTION for intravenous infusion. Do not add other medications to the ACETAMINOPHEN INJECTION bag.

The entire 100 mL bag of ACETAMINOPHEN INJECTION is not intended for use in patients weighing less than 50 kg. For doses less than 1000 mg, the appropriate dose must be withdrawn from the bag and placed into a separate container prior to administration. Using aseptic technique, withdraw the appropriate dose (weight-based) from an intact sealed ACETAMINOPHEN INJECTION bag 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. If transferred to 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 a single-use bag and the unused portion must be discarded.

**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 Supportive Care Drugs and Intravenous Infusion Solutions Compatible with ACETAMINOPHEN INJECTION**

<b>Drug</b>	
<ul style="list-style-type: none"> <li>• Buprenorphine hydrochloride</li> <li>• Butorphanol tartrate</li> <li>• Cimetidine hydrochloride</li> <li>• Dexamethasone sodium phosphate</li> <li>• Diphenhydramine hydrochloride</li> <li>• Dolasetron mesylate</li> <li>• Droperidol</li> <li>• Fentanyl citrate</li> <li>• Granisetron hydrochloride</li> <li>• Heparin sodium</li> <li>• Hydrocortisone sodium succinate</li> <li>• Hydromorphone hydrochloride</li> <li>• Hydroxyzine hydrochloride</li> <li>• Ketorolac tromethamine</li> </ul>	<ul style="list-style-type: none"> <li>• Lidocaine hydrochloride</li> <li>• Lorazepam</li> <li>• Mannitol</li> <li>• Meperidine hydrochloride</li> <li>• Methylprednisolone sodium succinate</li> <li>• Metoclopramide hydrochloride</li> <li>• Midazolam hydrochloride</li> <li>• Morphine sulfate</li> <li>• Nalbuphine hydrochloride</li> <li>• Ondansetron hydrochloride</li> <li>• Potassium chloride</li> <li>• Prochlorperazine edisylate</li> <li>• Sufentanil citrate</li> </ul>
<b>Infusion Solution</b>	
<ul style="list-style-type: none"> <li>• 5% dextrose injection</li> </ul>	<ul style="list-style-type: none"> <li>• 0.9% sodium chloride injection</li> </ul>

## 5 OVERDOSAGE

### **Signs and Symptoms**

In acute acetaminophen overdosage, dose-dependent potentially fatal hepatic necrosis is the most serious adverse event. Renal tubular necrosis, 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. 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, contact your regional poison control centre.

## **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**

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

<b>Route of Administration</b>	<b>Dosage Form / Strength/Composition</b>	<b>Non-medicinal Ingredients</b>
Intravenous	Solution 1000 mg / 100 mL (10 mg/mL)	mannitol, povidone K12, sodium dihydrogen phosphate dihydrate, sodium hydroxide (pH adjustment), water

ACETAMINOPHEN INJECTION is a sterile, clear, colorless to off-white/yellow, non-pyrogenic, 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 12 latex-free plastic bags of 100 mL. Each 100 mL of sterile solution contains 1000 mg acetaminophen, mannitol, povidone K12, sodium dihydrogen phosphate dihydrate, and water. The pH is adjusted with sodium hydroxide.

ACETAMINOPHEN INJECTION contains povidone K12, a low molecular weight povidone. Administered intravenously, low molecular weight povidone is expected to be readily excreted.

## **7 WARNINGS AND PRECAUTIONS**

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

### **Cardiovascular**

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

### **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.

### **Hepatic/Biliary/Pancreatic**

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death. 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 daily dose of acetaminophen (see **DOSAGE AND ADMINISTRATION**).

Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, and chronic malnutrition (low reserves of hepatic glutathione).

Acetylcysteine (N-acetyl-L-cysteine or NAC), the antidote for acetaminophen, may be considered in cases of overdose.

### **Renal**

Use caution when administering acetaminophen in patients with severe renal impairment (creatinine clearance  $\leq$  30 mL/min). Longer dosing intervals and/or a reduced total daily dose of acetaminophen may be warranted in these patients.

### **Hypersensitivity Reactions**

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 have been 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 **CONTRAINDICATIONS**).

### **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. ACETAMINOPHEN INJECTION should be given to a pregnant woman only if the benefit to the mother clearly outweighs the risk to the fetus.

### 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 has not been established.

ACETAMINOPHEN INJECTION is not recommended for this age group. The presence of hyperbilirubinaemia is associated with acetaminophen clearance reduction in neonates. ACETAMINOPHEN INJECTION contains povidone; there is limited data supporting its safe use in this age group (see **ACTION AND CLINICAL PHARMACOLOGY, 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 is supported by evidence from adequate and well-controlled studies of acetaminophen injection in adults and from pharmacokinetic and controlled studies in pediatrics.

### 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.

## 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 (86.9%) were treated with acetaminophen injection 1000 mg every 6 hours following surgery. Approximately 69% of acetaminophen injection-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  $\geq 5\%$ ) in adult patients treated with acetaminophen injection were nausea, vomiting, headache, and insomnia.

A total of 355 pediatric patients 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 6.8 and 7.1 days in 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  $\geq 5\%$ ) in pediatric patients treated with acetaminophen injection were nausea, vomiting, constipation, pruritus, agitation, and atelectasis.

## 8.2 Clinical Trial Adverse Reactions in Adults

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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Treatment-emergent adverse events (TEAEs) reported in  $\geq 1\%$  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  $\geq 1\%$  of Acetaminophen Injection-treated Adult Patients and at a Numerically Higher Frequency than Placebo**

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

AST = Aspartate aminotransferase; GGT = Gamma-glutamyl transferase

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.

### 8.3 Less Common Clinical Trial Adverse Reactions ( $> 0.3\%$ and $< 1\%$ ) in Adults

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, haemorrhoids, 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:** hypoglycaemia
- **Renal and urinary disorders:** pollakiuria
- **Respiratory, thoracic, and mediastinal disorders:** dyspnoea, cough, productive cough
- **Skin and subcutaneous tissue disorders:** erythema, night sweats
- **Vascular disorders:** hypertension

#### 8.4 Clinical Trial Adverse Reactions (Pediatrics)

##### Common: Reported by $\geq 1\%$ in Pediatrics

Treatment-emergent adverse events reported in  $\geq 1\%$  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:** anaemia (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 oedema (1.1%)
- **Infections and infestations:** wound infection (1.1%)
- **Investigations:** increased hepatic enzyme (1.1%)

- **Metabolism and nutrition disorders:** hypokalaemia (3.9%), hypomagnesaemia (3.9%), hypoalbuminaemia (1.7%), hypophosphataemia (1.4%), hypervolaemia (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 oedema (2.5%), wheezing (2.3%), stridor (2.0%), hypoxia (1.1%)
- **Skin and subcutaneous tissue disorders:** pruritus (7.9%), periorbital oedema (1.1%), rash (1.1%)
- **Vascular disorders:** hypotension (2.5%), hypertension (1.1%)

#### **Less Common: Reported by > 0.3% and < 1% in 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 oedema, generalized oedema, injection site extravasation, oedema
- **Hepatobiliary disorders:** hepatotoxicity
- **Infections and infestations:** abdominal abscess, incision site infection, laryngotracheitis, upper respiratory tract infection
- **Investigations:** decreased haemoglobin, decreased oxygen saturation, increased platelet count
- **Metabolism and nutrition disorders:** hypocalcaemia
- **Musculoskeletal and connective tissue disorders:** back pain, muscular weakness

- **Nervous system disorders:** brain oedema, 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, and thrombocytopenia.

## 9 DRUG INTERACTIONS

### 9.1 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.

### 9.2 Drug-Drug Interactions

#### Effects of other Substances on Acetaminophen

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.

The effects of ethanol are complex, because excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of acetaminophen.

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.

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 injection in patients on warfarin, more frequent assessment of INR may be appropriate in such circumstances.

### **9.3 Drug-Food Interactions**

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

### **9.4 Drug-Herb Interactions**

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

### **9.5 Drug-Laboratory Test Interactions**

Interactions with laboratory tests have not been established.

### **9.6 Drug-Lifestyle Interactions**

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.

## **10 ACTION AND CLINICAL PHARMACOLOGY**

### **10.1 Mechanism of Action**

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic agent that acts centrally. 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. Acetaminophen injection 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 following administration of a single intravenous dose of 15 mg/kg for the pediatric population (neonates, infants, children and adolescents) is comparable to that of administration of 1000 mg in adults, but the pharmacokinetic exposure is higher in neonates and infants (0 to <2 years of age). ACETAMINOPHEN INJECTION is not recommended for this age group. In addition, the presence of hyperbilirubinaemia is associated with acetaminophen clearance reduction in neonates.

ACETAMINOPHEN INJECTION contains low molecular weight povidone (povidone K12) and there is limited data supporting its safe use in neonates and infants. Povidone is an inactive compound which is not metabolized prior to its renal elimination, probably primarily through glomerular filtration. As glomerular filtration matures in infants by 3-5 months of age, povidone clearance might be somewhat slower in neonates and very young children, although the potential for povidone accumulation is unknown in this age group. The risk of accumulation of povidone K12 in older children and adults is low.

**Table 5 Summary of Acetaminophen Injection Pharmacokinetic Parameters<sup>a</sup>**

Subpopulation	C <sub>max</sub> , mcg/mL Mean (Standard Deviation)	t <sub>½</sub> , h Mean (Standard Deviation)	AUC <sub>0-T</sub> <sup>b</sup> , mcg×h/mL Mean (Standard Deviation)	CL, L/h/kg Mean (Standard Deviation)	V <sub>ss</sub> <sup>c</sup> , L/kg Mean (Standard Deviation)
<b>Neonates</b> (≤ 28 days old)	25 (4)	7.0 (2.7)	62 (11)	0.12 (0.04)	1.1 (0.2)
<b>Infants</b> (29 days to < 2 years old)	29 (24)	4.2 (2.9)	57 (54)	0.29 (0.15)	1.1 (0.3)
<b>Children</b> (2 years to < 12 years old)	29 (7)	3.0 (1.5)	38 (8)	0.34 (0.10)	1.2 (0.3)
<b>Adolescents</b> (12 years to ≤ 16 years old)	31 (9)	2.9 (0.7)	41 (7)	0.29 (0.08)	1.1 (0.3)
<b>Adults</b> (> 16 years old)	28 (21)	2.4 (0.6)	43 (11)	0.27 (0.08)	0.8 (0.2)

<sup>a</sup> Single dose mean

<sup>b</sup> AUC<sub>0-T</sub> was calculated after the first dose from 0 to 8 hours for neonates and 0 to 6 hours for infants, children 2 years of age and above, adolescents, and adults;

<sup>c</sup> V<sub>ss</sub> (Volume of distribution at steady state) determined using non-compartmental method

**Absorption and Distribution:** In adults, the pharmacokinetic profile of acetaminophen injection has been demonstrated to be dose proportional following administration of single 500, 650 and 1000 mg doses.

The maximum concentration (C<sub>max</sub>) of acetaminophen in plasma occurs at the end of the 15-minute intravenous infusion of acetaminophen injection. Compared to the same dose of oral acetaminophen elixir, the plasma C<sub>max</sub> following administration of acetaminophen injection is up to 70% higher and the T<sub>max</sub> 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 [AUC<sub>0-T</sub>, C<sub>max</sub>, terminal elimination half-life [T<sub>½</sub>], systemic clearance [CL], and volume of distribution at steady state [V<sub>ss</sub>]) 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 AUC<sub>0-T</sub> observed in children and adolescents is similar to adults, but higher in neonates and infants.

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.

## 11 STORAGE, STABILITY AND DISPOSAL

ACETAMINOPHEN INJECTION should be stored in the original container, including the metalized overpack, at room temperature (15 to 30°C). Do not refrigerate or freeze. Protect from light. Use immediately upon opening.

ACETAMINOPHEN INJECTION is for single use only: discard unused portion.

## PART II: SCIENTIFIC INFORMATION

### 12 PHARMACEUTICAL INFORMATION

#### Drug Substance

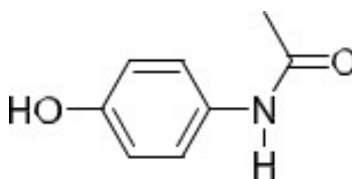
Proper name: acetaminophen

Chemical name: N-acetyl-p-aminophenol

Molecular formula:  $C_8H_9NO_2$

Molecular mass: 151.16

Structural formula:



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

## 13 CLINICAL TRIALS

### 13.1 Trial Design and Study Demographics

The efficacy of acetaminophen injection was evaluated for the treatment of acute pain in adults in two pivotal, randomized, double-blind, placebo-controlled clinical trials in patients with postoperative pain and in one pivotal, randomized, double-blind, controlled clinical trial for the treatment of fever in adults (see **Table 6**).

**Table 6 Summary of Patient Demographics for Clinical Trials in Post-operative Pain and Fever**

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Sex
<b>Study 1</b> Postoperative pain following total hip or knee replacement	Randomized, double-blind, 3-parallel-group, active- and placebo-controlled	4 doses q6h over 24 hours. Treatment Groups: 1 g IV acetaminophen, 2 g IV propacetamol, or IV placebo	n = 151	60.1 years (22 – 87)	M: 51% F: 49%
<b>Study 2</b> 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% F: 81%
<b>Study 3</b> 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%

#### Adult Acute Pain (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.

#### Adult Acute Pain (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, 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.

#### Adult Fever (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.

### Adult Fever (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.

### Pediatric Acute Pain and Fever

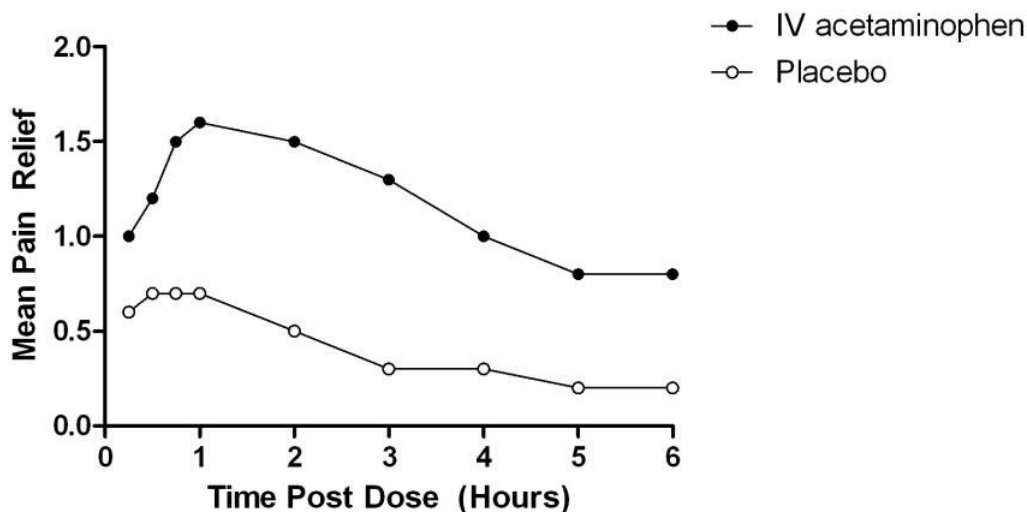
Acetaminophen injection was studied in 355 patients across the full pediatric age strata, from premature neonates ( $\geq 32$  weeks post menstrual age) to adolescents, in two active-controlled and three open-label safety and pharmacokinetic trials.

## 13.2 Study Results

### Adult Acute Pain (Study 1)

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**



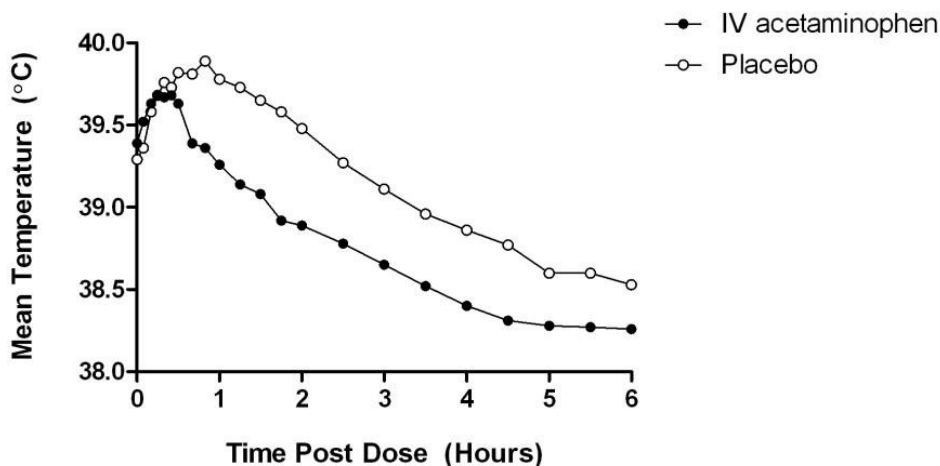
### Adult Acute Pain (Study 2)

A statistically significant difference of  $p = 0.0068$  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.

### Adult Fever (Study 3)

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 (Study 4)

The single-dose endotoxin-induced fever supporting study indicated 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

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 injection 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.

## 14 NON-CLINICAL TOXICOLOGY

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.

## Repeat-Dose Toxicity Studies

Acetaminophen injection 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.

## Mutagenesis

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 maximum human daily dose (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.

## 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.

### **Carcinogenesis**

Long-term studies in mice and rats have been completed by the U.S. 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).

### **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.

## **15 SUPPORTING PRODUCT MONOGRAPHS**

Ofirmev® (1000 mg / 100 mL), submission control 212275, Product Monograph, Mallinckrodt Hospital Product Inc. January 30, 2018.