เอกสารกำกับยาสำหรับแพทย์ฉบับภาษาอังกฤษ

TYLENOL® 8 HOUR
EXTENDED-RELEASE TABLETS

1. NAME OF THE MEDICINAL PRODUCT

INTERNATIONAL NON-PROPRIETARY NAME

Paracetamol (INN) / Acetaminophen (USAN)

Note: Acetaminophen hereafter will be referred to as paracetamol.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tylenol 8 Hour caplet, consisting of 2 special layers, contains paracetamol (acetaminophen) 650 mg.

3. PHARMACEUTICAL FORM

Extended-Release Tablets. White film coated caplet debossed with "TYLENOL" over "ER" on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

- The medicine's generic name is paracetamol. It belongs to the class of pain reliever and fever reducer.
- This medicine is used to reduce fever, relieve mild to moderate pain, including headache, aches and pains associated with the common cold, toothache, period pain, muscle pain, back pain, arthritis pain.

4.2. Posology and Method of Administration

This product is the particular dosage form where the drug is gradually released and only designed for taking 2 caplets per time. Must strictly use the product according to the following dosage and period:

Dosage

- Adult from 18 years of age and older with body weight from 44 kg upward: take two caplets per time, at least 8 hours between doses, only while pain or fever persists.
- People with body weight less than 44 kg or less than 18 years of age: do not use this product due to the overdose which may lead to liver toxicity.

Directions of use

Swallow as a whole; Do not break, chew, crush, divide, or dissolve because overdose may occur.

4.3. Contraindications

Hypersensitivity to paracetamol or to any of the ingredients. (see Section 4.8)

4.4. Special Warnings and Special Precautions for Use

- Overdose warning*: Taking more than the recommended dose (overdose) may result in liver damage*. *In case of overdose, get medical help immediately. Quick medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.*

- Alcohol Warning: *Chronic alcohol users should ask their physician whether they should take paracetamol or other pain relievers or fever reducers* (adult products).

- *Patients with hepatic disease should consult a physician before use.* (see Section 5.2.3)

- Serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens - Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported very rarely in patients receiving paracetamol. Patients should be informed about the signs of serious skin reactions and *use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity*.

- *Do not use with any other product containing paracetamol*.

- *If symptoms persist or get worse, or if new symptoms occur, stop use and consult a physician.*

- *If you have high blood pressure, do not sue this product longer than directed on the label unless directed by a doctor.*

4.5. Interactions with Other Medicinal Products and Other Forms of Interaction

4.5.1. WARFARIN-LIKE COMPOUNDS

For most patients, occasional use of paracetamol generally has little or no effect on the INR in patients on chronic warfarin therapy; however, there has been controversy regarding the possibility of paracetamol potentiating the anticoagulant effects of warfarin and other coumarin derivatives. Consumers should be instructed to *ask a physician or pharmacist before use if they are taking the blood thinning drug warfarin or other coumarin derivatives.*

4.5.2. FLUCLOXACILLIN

High anion gap metabolic acidosis from pyroglutamic acid (5-oxoprolinemia) has been reported with concomitant use of therapeutic doses of paracetamol and flucloxacillin. Patients reported to be most at risk are elderly females with

underlying disease such as sepsis, renal function abnormality, and malnutrition. Most patients improve after stopping one or both of the drugs. Consumers should be instructed to *ask their health care provider before use if they are taking the antibiotic flucloxacillin*.

4.6. Pregnancy and Lactation

There are no adequate and well-controlled clinical studies in pregnant or breastfeeding women for paracetamol.

When given to the mother in labeled doses, paracetamol crosses the placenta into fetal circulation as early as 30 minutes after ingestion and is effectively metabolized by fetal sulfate conjugation. When taken as directed, paracetamol does not adversely affect the pregnant mother or fetus.

Paracetamol is excreted in breast milk in low concentrations (0.1% to 1.85% of the ingested maternal dose). Maternal ingestion of paracetamol in labeled doses does not present a risk to the nursing infant.

This product should not be used during pregnancy or lactation unless the potential benefit of treatment to the mother outweighs the possible risks to the developing fetus/nursing infant. *Ask a physician before use if you are pregnant or breastfeeding.*

4.7. Effects on Ability to Drive or Use Machines

It is not known if paracetamol has an effect on the ability to drive and use machines. Clinical data suggest that paracetamol does not affect neuromuscular performance.

4.8. Undesirable Effects

Clinical Trial Data

The safety of single-ingredient paracetamol from clinical trial data in adults is based on 59 randomized, placebo-controlled clinical trials evaluating treatment of pain and fever.

No adverse events occurring at the rate of >1% over placebo were identified for single-ingredient paracetamol in randomized, placebo-controlled clinical trials evaluating treatment of pain and fever in adults or children.

Post Marketing Data

Adverse drug reactions (ADRs) identified during post marketing experience with paracetamol are included in Table 1. The frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1,000 and < 1/100
Rare	≥ 1/10,000 and < 1/1,000

Very rare	< 1/10,000
Not known	(cannot be estimated from the available data)

In Table 1, ADRs are presented with ADR frequency categories estimated from spontaneous reporting rates where the numerator represents the total number of reported Company ADRs under a given PT or medical concept and the denominator represents exposure data calculated from sales data.

Table 1: Adverse Drug Reactions Identified During Post Marketing Experience with Paracetamol by Frequency Category Estimated from Spontaneous Reporting Rates

SOC Frequency Category	Adverse Event Preferred Term
Immune System Disorders	
Very rare	*Anaphylactic reaction*
Very rare	*Hypersensitivity*
Skin and Subcutaneous Tissue Disorder	
Very rare	*Fixed eruption*
Very rare	*Rash pruritic*
Very rare	*Rash*
Very rare	*Urticaria*
Investigations	
Very rare	*Transaminases increased*[a]

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

4.9. Overdose

Hepatobiliary Disorders

If a paracetamol extended-release product is involved or if the exact formulation is not known, it is recommended to obtain an additional plasma paracetamol level 4 to 6 hours following the initial paracetamol level as these levels will continue to rise with the extended-release products and may alter treatment decisions.

In adults and adolescents (⩾12 years of age), hepatic toxicity may occur following ingestion of greater than 7.5 to 10 g over a period of 8 hours or less. Fatalities are infrequent (less than 3-4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children (<12 years of age), an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity. Early symptoms following a potentially hepatotoxic overdose may include: Anorexia, nausea, vomiting,

diaphoresis, pallor and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.Serious toxicity or fatalities have been extremely infrequent following an acute paracetamol overdose in young children, possibly because of differences in the way they metabolize paracetamol.

Table 2 shows the clinical events associated with paracetamol overdose that if seen with overdose are considered expected, including fatal events due to fulminant hepatic failure or its sequelae.

Table 2: Adverse Drug Reactions Identified with Overdose of Paracetamol

System Organ Class	Preferred Term
Metabolism and Nutrition Disorders	Decreased appetite
Gastrointestinal Disorders	Abdominal discomfort
	Nausea
	Vomiting
Hepatobiliary Disorders	Acute hepatic failure
	Hepatic necrosis
	Hepatomegaly
	Jaundice
	Liver tenderness
General Disorders and Administration Site Conditions	Hyperhidrosis
	Malaise
	Pallor
Investigations	Blood bilirubin increased
	Blood lactic acid increased
	Blood phosphorus increased
	Hepatic enzymes increased
	International normalised ratio increased
	Prothrombin time prolonged

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

Expected sequelae to acute hepatic failure associated with paracetamol overdose include the following: Bacterial infection, fungal infection, sepsis, coagulopathy, disseminated intravascular coagulation, thrombocytopenia, hypoglycaemia, hypophosphatemia, lactic acidosis, metabolic acidosis, brain oedema, coma (with

massive paracetamol overdose or multiple drug overdose), encephalopathy, cardiomyopathy, hypotension, respiratory failure, gastrointestinal haemorrhage, pancreatitis, acute kidney injury, and multiple organ dysfunction syndrome.

Blood and Lymphatic Disorders

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

Keep out of reach of children. In the event of overdose, get medical help or contact a Poison Control Center right away.

5. PHARMACOLOGICAL PROPERTIES

Chemical Name
N-acetyl-p-aminophenol

Molecular Weight
151.16 g/mol

5.1. Pharmacodynamic Properties

Paracetamol is a centrally acting, non-opiate, non-salicylate analgesic. Paracetamol is a clinically proven analgesic/antipyretic, and it is thought to produce analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulating center. Single-dose studies (12.5 mg/kg) of paracetamol in febrile children showed an onset of fever reduction within 15 to 30 minutes.

5.2. Pharmacokinetic Properties

5.2.1. ABSORPTION

5.2.1.1 Extended release
Each bilayered paracetamol extended-release, 650 mg caplet contains 325 mg of immediate-release paracetamol on one side and 325 mg of paracetamol in a matrix formulation designed to slowly release on the other side. Following administration of a single dose of two 650 mg extended-release tablets, paracetamol absorption is initially rapid and comparable to the immediate-release tablets. The average maximal plasma concentrations occur within 0.5 to 3 hours due to the slowly dissolving layer, and range from 6.9 to 14.1 µg/mL among individuals.

5.2.1.2 Food Effects
Although maximum concentrations of paracetamol are delayed when administered with food, the extent of absorption is not affected. Paracetamol can be taken independently of meal times.

5.2.2. DISTRIBUTION

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is 0.7 to 1 L/kg in children and

adults. A relatively small proportion (10% to 25%) of paracetamol is bound to plasma protein.

5.2.3. METABOLISM

Paracetamol is primarily metabolized in the liver and involves three main pathways: conjugation with glucuronide; conjugation with sulfate; and oxidation via cytochrome P450 enzyme pathway. The oxidative pathway forms a reactive intermediate, which is detoxified by conjugation with glutathione to form inert cysteine and mercapturic acid metabolites. The principal cytochrome P450 isoenzyme involved *in vivo* appears to be CYP2E1, although CYP1A2 and CYP3A4 were considered minor pathways based on *in vitro* microsomal data. Subsequently, both CYP1A2 and CYP3A4 were found to have negligible contribution *in vivo*.

In adults, the majority of paracetamol is conjugated with glucuronic acid and, to a lesser extent, with sulfate. The glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates. In adults with liver impairment of differing severity and etiology, several metabolism studies have demonstrated that the biotransformation of paracetamol is similar to that in healthy adults, but somewhat slower. Importantly, consecutive daily dosing at 4000 mg per day induces glucuronidation (a nontoxic pathway) in healthy and liver-impaired adults, resulting in increased total clearance of paracetamol over time and limited plasma accumulation.

5.2.4. ELIMINATION

The elimination half-life of paracetamol is about 1 to 3.5 hours. It is approximately one hour longer in neonates and in cirrhotic patients. Paracetamol is eliminated from the body as glucuronide (45-60%) and sulfate (25-35%) conjugates, thiols (5-10%) as cysteine and mercapturate metabolites, and catechols (3-6%) that are excreted in the urine. Renal clearance of unchanged paracetamol is about 3.5% of the dose.

5.3. Pre-clinical Safety Data

Summary:

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, carcinogenicity and toxicity to reproduction and development.

5.3.1. GENERAL TOXICOLOGY

A number of acute, sub-acute, and chronic toxicity studies in animals show that the toxic effects of paracetamol appear only at amounts well above therapeutic doses.

5.3.2. GENETIC TOXICOLOGY

Considering in vitro and in vivo studies, a comprehensive and conclusive review, accepted by the Committee for Proprietary Medical Products (CPMP) of the European Union reports that genotoxic effects of paracetamol appear only at dosages inducing pronounced liver and bone marrow toxicity and that the threshold level for genotoxicity is not reached at the labeled dosage.

5.3.3. CARCINOGENICITY

Based on several long-term studies, paracetamol does not indicate a carcinogenic potential at non-hepatotoxic dose levels.

5.3.4. TERATOGENICITY

Paracetamol was not found to be teratogenic in rats or mice.

5.3.5. FERTILITY

The doses at which reproductive toxicity or effects on fertility are seen are much higher than the recommended doses in humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Excipients: Powdered cellulose; Corn starch; Sodium starch glycolate; Pregelatinized starch; Microcrystalline cellulose; Hydroxyethyl cellulose; Povidone; Magnesium stearate; Opadry white; Carnauba wax, Purified water.

6.2. Incompatibilities

Not known.

6.3. Shelf Life

24 months.

See expiry date after the word "Exp. Date" on the carton.

Do not use this medicine beyond the expiry date printed on the packaging.

6.4. Special Precautions for Storage

Do not store above 30°C.

Keep out of reach of children.

6.5. Nature and Contents of Container

Box of 1 and 5 blisters, each blister contains 10 caplets.

6.6. Instructions for Use and Handling and Disposal

UNLESS INSTRUCTED OTHERWISE, DO NOT DISPOSE OF UNUSED MEDICINES BY EMPTYING THEM INTO YOUR SINK, TOILET OR STORM DRAIN.

Manufactured by	**Marketing Authorization Numbers**	**Date of Authorization**

McNeil Consumer Healthcare, division of Johnson & Johnson, Inc. Ontario, Canada Primary packaged, Secondary packed and Final Released by PT. Integrated Healthcare Indonesia, Jakarta Timur, Indonesia	1C 15056/65 (N)	5-May-2022

Date of revision of the text:

8 February 2024 (CCDS version 8, 31-May-2023)

Imported by

Johnson and Johnson (Thailand) Ltd.

Bangkok, Thailand

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Warnings according to Ministry of Public Health announcement

1. Paracetamol should not be taken in excess of recommended dose, otherwise it will cause liver poisoning. It should not be taken for more than 5 consecutive days.

2. Do not take this drug with other drug containing paracetamol. Doing so will lead to overdose.

3. Those who regularly consume alcohol or suffer from liver or kidney disease should consult their doctor or pharmacist before taking this drug.

4. If, after taking this drug, face, eyelid or lips are swollen, rash or spots come up, dizziness, itches and skin peeling off occur, the drug should be discontinued, and medical consultation should immediately be sought after.