

”פורמט עלון זה נקבע ע”י משרד הבריאות ותוכנו נבדק ואושר על ידי”

# ACETYLSALICYLIC ACID, PARACETAMOL & CAFFEINE

CAPLETS

## Composition

Each plain biconvex caplet contains:

### Active Ingredient

Acetylsalicylic acid	250 mg
Paracetamol	250 mg
Caffeine	65 mg

### Other Ingredients

Microcrystalline cellulose, crospovidone, stearic acid, silicon dioxide, color [hydroxypropyl methylcellulose, FD&C red #40, FD&C yellow #6, polyethylene glycol 400, titanium dioxide, polysorbate 80].

## Mechanism of Action

This preparation provides a powerful, quick-acting analgesia. The synergistic combination of acetylsalicylic acid, paracetamol and caffeine produces greater analgesia than that produced by each component alone. Administered alone, this preparation relieves pain associated with migraine headache, as well as pain associated with other conditions (see Indications).

## Indications

For temporary relief of the pain of headache, mild to moderate pain associated with migraine headache, pain due to sinusitis or colds, muscular aches, pain of menstrual discomfort, toothaches and minor arthritis pain and pain accompanied by fever.

## Contraindications

- Known hypersensitivity to any ingredient of the preparation.
- Hemophilia
- Bleeding ulcers
- Pregnancy and lactation (see Warnings).
- Hemorrhagic states
- Hypersensitivity to other nonsteroidal anti-inflammatory agents which inhibit prostaglandin synthesis (see also Warnings).
- Newborn or premature infants
- Asthma in combination with nasal polyps
- In patients that suffered in the past from the following side effects after taking an analgesic or a fever lowering medicine: urticaria, swelling of the face, asthma, shock.
- In children and adolescents below 20 years of age, for diseases accompanied by fever, such as chicken pox or flu.

## Warnings

### For Acetylsalicylic Acid

Acetylsalicylic acid may precipitate bronchospasm and induce asthmatic attacks in susceptible patients (see Contraindications).

***Reye Syndrome-Salicylate Association:*** The use of salicylates, in particular acetylsalicylic acid, in children and adolescents up to the age of 20, with viral febrile illness, especially influenza or chickenpox, may be associated with the development of Reye's syndrome—a rare, acute, life-threatening condition, characterized by vomiting and lethargy that may progress to delirium and coma.

Chronic alcohol users (3 or more alcoholic drinks per day) should be warned that they may be at an increased risk of stomach bleeding from use of acetylsalicylic acid.

Acetylsalicylic acid should be used with caution in patients with asthma or allergic disorders. Continuous prolonged use of acetylsalicylic acid should be avoided in the elderly because of the risk of gastrointestinal bleeding

***Hypersensitivity:*** Cross-sensitivity may exist between acetylsalicylic acid and other non-steroidal anti-inflammatory drugs which inhibit prostaglandin synthesis. This cross-sensitivity does not appear to occur with non-acetylated salicylates such as sodium salicylate, salicylamide or choline salicylate.

Acetylsalicylic acid hypersensitivity is more prevalent in patients with asthma, nasal polyps or chronic urticaria, swelling of face or lips.

***Use in Surgery:*** Use of salicylates should be avoided, if possible, one week prior to surgery, to reduce the likelihood of post-operative bleeding.

#### *For Caffeine*

Consumption of large quantities of products containing caffeine may reactivate preexisting duodenal ulcers.

#### *For Paracetamol*

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease. Patients should be advised not to take other paracetamol-containing products concurrently.

#### *Use in Pregnancy*

Safety of use in pregnancy has not been established.

The use of acetylsalicylic acid during pregnancy should be avoided since it may produce adverse reactions in the mother, such as anemia, antepartum or postpartum hemorrhage, prolonged gestation and prolonged labor.

Acetylsalicylic acid readily crosses the placenta. It may cause constriction of the ductus arteriosus and other untoward effects in the fetus.

The use of acetylsalicylic acid during the later stages of pregnancy has been associated with the following fetal adverse effects: low birth weight, increased incidence of intracranial hemorrhage in premature infants, still-births and neonatal death. In high dosage and continuous use, acetylsalicylic acid is a possible teratogen.

#### *Use in Lactation*

The safety of use in lactation has not been established. It is known that acetylsalicylic acid is excreted in breast milk. Paracetamol also appears in very low concentrations in breast milk. Therefore this product should not be used in nursing women unless, in the judgment of the physician, the potential benefits to the mother outweigh the possible hazards to the fetus.

#### *Use in Pediatrics*

This preparation is not recommended for use in children under 12 years of age.

### *Use in Patients with Impaired Hepatic or Renal Function*

Because of the paracetamol and acetylsalicylic acid components, this product should be administered with care to patients with impaired hepatic (especially in patients with collagen diseases—a warning related to acetylsalicylic acid) or renal function.

## **Adverse Reactions**

### *Adverse Reactions in Connection with Acetylsalicylic Acid*

Gastric irritation may occur.

Some patients may exhibit notable sensitivity to acetylsalicylic acid which may provoke various reactions including urticaria and other skin eruptions, angioneurotic edema, rhinitis, severe paroxysmal bronchospasm, dyspnea and tinnitus. Acetylsalicylic acid increases bleeding time, decreases platelet adhesiveness and modifies fibrinolysis. In large doses, it may cause hypoprothrombinemia.

### *Adverse Reactions in Connection with Paracetamol*

Adverse reactions of paracetamol are usually mild, though hematological reactions have been reported in rare cases.

Skin eruptions may occur as an allergic reaction.

Long term use and/or high dosage may cause liver and kidney damage.

### *Adverse Reactions in Connection with Caffeine*

Caffeine may cause nausea, abdominal pain, diarrhea, insomnia, restlessness, nervousness, tinnitus, muscular tremor and palpitations.

## **Precautions**

### *For Acetylsalicylic Acid*

Acetylsalicylic acid should be used with great caution in patients prone to dyspepsia or known to have a lesion of the gastric mucosa.

Acetylsalicylic acid should be used with caution in the following situations:

- in dehydrated patients, particularly children
- in patients with coagulation or platelet function disorders.
- in patients with gout (see Drug Interactions and Diagnostic Interference)

### *For Paracetamol*

If a sensitivity reaction occurs, discontinue use.

### *For Acetylsalicylic Acid and Paracetamol*

Paracetamol and aspirin may cause liver damage (additive effect with alcohol) and stomach bleeding

## **Drug Interactions**

### *For Acetylsalicylic acid*

**Acetylsalicylic Acid/Alcohol/Anti-inflammatory Agents:** The ulcerogenic effects may be increased when used concurrently.

**Acetylsalicylic Acid/Paracetamol:** Prolonged use in high dosage of a combination of these two drugs, with or without other non-steroidal anti-inflammatory drugs, increases the risk of nephropathy.

**Acetylsalicylic Acid/Corticosteroids:** Corticosteroids increase salicylate clearance, thus reducing serum salicylate levels.

**Acetylsalicylic Acid/Phenothiazines:** Concurrent use may mask the symptoms of salicylate-induced ototoxicity, such as dizziness, vertigo and tinnitus.

**Acetylsalicylic Acid/Oral Anticoagulants:** Concurrent use may cause possible potentiation of the hypoprothrombinemic effects.

**Acetylsalicylic Acid/Oral Hypoglycemics/Insulin:** The hypoglycemic effect may be increased when these drugs are used concurrently.

**Acetylsalicylic Acid/Methotrexate:** Drug displacement from binding sites leading to toxic plasma concentration of methotrexate may occur when these drugs are used concurrently.

**Acetylsalicylic Acid/Probenecid/Sulfinpyrazone:** The uricosuric effects of these agents may be affected when used concurrently with salicylates (see Diagnostic Interference).

**Acetylsalicylic Acid/Urinary Alkalinizers:** Alkalinized urine leads to decreased plasma levels of acetylsalicylic acid because of increased excretion. Withdrawal of these medications from a patient stabilized on a salicylate may increase the plasma levels of acetylsalicylic acid to a toxic level.

**Acetylsalicylic Acid/Urinary Acidifiers:** Acidified urine leads to increased plasma levels of acetylsalicylic acid because of decreased excretion. Addition of these medications to patients stabilized on acetylsalicylic acid may lead to toxic acetylsalicylic acid levels.

**Acetylsalicylic Acid/Diuretic Drugs:** acetylsalicylic acid may inhibit or minimize the diuretic effects of spironolactone and furosemide.

#### *For Paracetamol*

**Paracetamol/Oral Anticoagulants:** Regular administration of paracetamol may enhance the activity of coumarin anticoagulants when given concurrently. Occasional doses have no significant effect.

**Paracetamol/ Hepatic Enzyme-Inducing Agents/Hepatotoxic Medications/ Alcohol:** Concurrent administration of enzyme inducers and paracetamol may decrease the therapeutic effect of paracetamol, probably because of increased metabolism resulting from induction of hepatic microsomal enzyme activity.

The risk of hepatotoxicity with single toxic doses or prolonged use of high doses of paracetamol may be increased in alcoholics or in patients taking other hepatotoxic medications

**Paracetamol/ Salicylates/ Other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):** Chronic high-dose administration of paracetamol with salicylates and/or other non-steroidal anti-inflammatory drugs increases the risk of analgesic nephropathy.

**Paracetamol/ Zidovudine:** Paracetamol may competitively inhibit the hepatic glucuronidation and decrease the clearance of zidovudine. Zidovudine may also inhibit the hepatic glucuronidation of paracetamol. Concurrent use should be avoided, because the toxicity of either or both medications may be potentiated.

#### *For Caffeine*

**Caffeine/Bronchodilators/Caffeine Containing Beverages:** Concomitant administration may result in additive CNS stimulation. Too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat.

### **Diagnostic Interference**

#### *For Acetylsalicylic Acid*

The Gerhardt test for urine acetoacetic acid may give false-positive test results, because the reaction with ferric chloride produces a reddish color that persists after boiling.

Urine 5-hydroxyindoleacetic acid (5-HIAA) determination may give false test results with acetylsalicylic acid when the fluorescent method is used

Urine vanillylmandelic acid (VMA) levels may be falsely increased or decreased, depending on the method used.

Urine phenolsulfonphthalein (PSP) concentrations may be decreased because of the competition of salicylates with PSP for renal tubular secretion.

Bleeding time may be prolonged by acetylsalicylic acid for 4-7 days because of suppressed platelet aggregation.

Serum potassium concentration may be decreased because of increased potassium excretion caused by direct effect on renal tubules.

Serum uric acid concentrations may be increased or decreased, depending on salicylate dosage. Salicylate concentrations below 100-150 µg/ml increase serum uric acid concentrations, while salicylate concentrations above 100-150 µg/ml decrease uric acid concentrations.

Serum uric acid values may be falsely increased with colorimetric acid methods when plasma salicylate concentrations exceed 130 µg/ml; the uricase acid method is not affected.

Fehling's test for urine sugar may give false-positive test results with doses of salicylates equivalent to, or exceeding 2.4 g of acetylsalicylic acid per day.

#### *For Paracetamol*

**Blood Glucose Determinations:** May be falsely decreased when measured by the glucose oxidase/ peroxidase method, but probably not when measured by the hexokinase/ glucose-6-phosphate dehydrogenase (G<sub>6</sub>PD) method.

**Serum Uric Acid Determinations:** Falsely increased values may occur when the phosphotungstate uric acid test method is used.

**Urine 5-hydroxyindoleacetic Acid (5-HIAA) Determinations:** Qualitative screening tests using nitrosonaphthol reagent may produce false-positive test results. The quantitative test is unaffected.

**Pancreatic Function Test Using Bentiromide:** Administration of paracetamol prior to the bentiromide test will invalidate the test results, because paracetamol is also metabolized to an arylamine and will therefore increase the apparent quantity of para-aminobenzoic acid (PABA) recovered. It is recommended that paracetamol be discontinued at least 3 days prior to administration of bentiromide.

#### *For Caffeine*

Caffeine may interfere with laboratory determinations of bilirubin, fasting blood glucose, uric acid in blood, and catecholamines and 5-hydroxy indoleacetic acid in urine.

## **Dosage and Administration**

### *Adults and Children Over 12 Years of Age*

2 caplets with a full glass of water after meal every 6 hours while symptoms persist, not to exceed 8 caplets in 24 hours. Not to be taken for more than 48 hours for the pain of migraine.

*Note:* The patient should be instructed not to lie down for 15-30 minutes following drug intake in order to reduce the risk of esophageal irritation and ulceration.

## **Overdosage**

### *For Acetylsalicylic Acid*

**Manifestations:** Acetylsalicylic acid poisoning is most commonly manifested by acid-base disturbances, hypoprothrombinemia, hyperthermia and gastroenteritis.

The acid-base disturbances are the most dangerous. Respiratory alkalosis appears first, followed by metabolic acidosis. Severe poisoning is associated with initial serum salicylate levels above 400 µg/ml. The clinical picture includes hyperpnea, flushed face, hyperthermia, tinnitus, abdominal pain, headache, vomiting, dehydration, spontaneous bleeding, twitching, convulsion, dizziness, confusion, severe drowsiness, pulmonary edema, uremia and coma.

In acetylsalicylic acid intoxication, ketones and glucose may be present in the urine. Phenistix or a ferric chloride test aids in diagnosis of acetylsalicylic acid ingestion and possible overdosage.

**Treatment:** For mild intoxication, emptying the stomach by emesis, aspiration, or gastric lavage with 5% sodium bicarbonate solution will usually suffice. Patients suffering from severe intoxication (a plasma-salicylate level above 500 µg/ml in adults or above 300 µg/ml in children) should undergo gastric lavage together with forced diuresis by intravenous infusions of saline with sodium bicarbonate, compound sodium lactate injection or dextrose solution.

An osmotic diuretic may be necessary to enhance the diuresis in some patients.

Potassium salts should be given to correct deficiencies.

Electrolyte and acid-base balance should be monitored regularly.

Hemodialysis or peritoneal dialysis may be necessary in extreme cases, particularly if there is cardiac, renal or respiratory impairment. Assisted respiration may be necessary.

In patients suffering from acute allergic reactions to acetylsalicylic acid, adrenaline and corticosteroids followed by an antihistamine should be administered.

#### *For Paracetamol*

**Manifestations:** In massive overdosage, paracetamol may cause hepatic toxicity. In adults and adolescents, hepatic toxicity has been rarely reported following ingestion of acute overdose of less than 7.5 –10 g. Fatalities are infrequent (less than 3-4% of untreated cases) and have been rarely reported with overdoses of less than 15 g. Early symptoms following a potentially hepatotoxic overdose may include nausea, vomiting, stomach pain, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48-72 hours post-ingestion.

Serious toxicity or fatalities are extremely infrequent in children, possibly due to differences in the way they metabolize paracetamol. An acute overdosage of less than 150 mg/kg bodyweight in children has not been associated with hepatic toxicity.

**Treatment:** Regardless of the quantity of paracetamol reported or assumed to have been ingested, N-acetylcysteine should be administered immediately, if 24 hours or less have elapsed from the time of ingestion.

An initial dose of 150 mg N-acetylcysteine/kg body weight is infused I.V. in 200 ml of 5% Dextrose Injection over 15 minutes. This is followed by I.V infusion of 50 mg N-acetylcysteine/kg body weight in 500 ml of 5% Dextrose Injection over the next 4 hours, and 100 mg N-acetylcysteine/kg body weight in 1 liter of 5% Dextrose Injection over the next 16 hours (providing a total dose of 300 mg/kg body weight of N-acetylcysteine over 20 hours).

In addition to N-acetylcysteine administration, it is recommended that the stomach be emptied promptly by lavage, or by induction of emesis with syrup of ipecac.

A serum paracetamol assay should be obtained as early as possible, but not less than 4 hours following ingestion. If plasma level falls above the lower treatment line on the paracetamol overdose nomogram, acetylcysteine therapy should be continued.

Liver function tests should be performed initially, and repeated at 24-hour intervals.

#### **Registration Number**

131.35.30995.00

#### **Presentation**

Packs of 16, 20, 30, and 50 caplets.

#### **Manufacturer**

Teva Pharmaceutical Industries Ltd  
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