PARACETAMOL

NAPREX®

150 mg/mL Solution for Injection (IM/IV)
(300 mg/2 mL Injection)

Analgesic/Antipyretic

FORMULATION
Each mL contains:
Paracetamol ..... 150 mg

PRODUCT DESCRIPTION
Paracetamol (Naprex®) 150 mg/mL Solution for Injection (IM/IV) (300 mg/2 mL Injection) is a clear, colorless to slightly yellow solution for injection, free from extraneous matter, filled in a 2 mL amber ampule with white dot.

PHARMACODYNAMICS/MECHANISM OF ACTION
Paracetamol exhibits analgesic and antipyretic activity by inhibiting prostaglandin synthesis. It produces analgesia by elevating the pain threshold and antipyresis through its action on the hypothalamic heat-regulating center.

In therapeutic doses, the analgesic and antipyretic action of paracetamol is comparable to that of aspirin. Paracetamol does not adversely affect platelet function and hemostasis.

PHARMACOKINETICS
The pharmacokinetics of paracetamol after a single 1000 mg intravenous dose (as a 20 mg/mL solution over 5 minutes) was measured in six healthy male subjects. Data was interpreted as a two-compartment open model. The decline in plasma paracetamol concentration (C_t) after intravenous administration appeared to be bi-exponential. An initial rapid fall over the first 1.5 hours was followed by a mono-exponential decline over the remaining 4.5 hours of observation. The half-life ($T_{1/2\alpha}$) of the first exponential ranged from 0.15 to 0.53 hour (mean = 0.32 hour) and that of the second exponential ($T_{1/2\beta}$) ranged from 2.24 to 3.30 hours (mean = 2.50 hours). Plasma clearance (V_p) ranged from 264 to 505 mL/min (mean = 352±40 mL/min). The area under the plasma concentration time curve (AUC) was measured to be 50.5±5.7 µg/mL.h.

Paracetamol is not bound to plasma proteins by any extent. The concentrations of paracetamol in saliva are similar to those in plasma. Concentrations in whole blood are up to 20% higher and in breast milk about 20% lower than the plasma concentration. Paracetamol crosses the placenta.

Paracetamol is extensively metabolized in the liver. About 80 to 85% of paracetamol in the body undergoes conjugation principally with glucuronic acid and to lesser extent with sulfuric acid. Small quantities of paracetamol are metabolized by a cytochrome P-450 microsomal enzyme to a reactive intermediate metabolite (N-acetyl-p-benzoquinoneimine) which is further metabolized via conjugation with glutathione and ultimately excreted in urine as mercapturic acid and cysteine conjugates of paracetamol. This intermediate metabolite is suggested to be responsible for paracetamol-induced liver necrosis; high doses of paracetamol may deplete glutathione so that inactivation of this toxic metabolite is decreased. At high paracetamol doses, the capacity for conjugation with glucuronic acid and sulfuric acid may be exceeded, resulting in increased metabolism of paracetamol by alternative pathways. Following a hepatotoxic overdose, the clearance of paracetamol is reduced and the half-life increased. Prolongation beyond four hours usually indicates impending liver damage.

Two to five percent of a therapeutic dose of paracetamol is excreted unchanged in the urine. Its renal clearance is about 10 mL/min and is weakly dependent on urine flow rate but not on pH.

INDICATIONS
- Useful in conditions where a rapid predictable blood level is required as in high grade fever in children predisposed to febrile convulsions.
- High grade fever in patients who cannot tolerate oral medications.
- As an analgesic, in postoperative patients where oral medication is not possible.

DOSAGE AND ADMINISTRATION
Recommended Dose: 10 mg/kg body weight/dose, to be given by slow intravenous (IV) push or by deep intramuscular (IM) injection, every 4 to 6 hours while symptoms persist, or approximately as follows:

AGE	IM/IV DOSE EVERY 4 TO 6 HOURS
Children:	
Below 6 months	0.25 to 0.5 mL
6 to 12 months	0.5 to 0.75 mL
1 to 2 years	0.75 to 1 mL
3 to 6 years	1 to 1.25 mL
7 to 12 years	1.25 to 2 mL
Adults:	2 to 4 mL
Or, as directed by a physician	

Do not exceed 5 doses in each 24-hour period and do not give for more than five days unless directed by a physician.

Note: Strict aseptic technique should be observed when drawing up the contents of the ampule. If injection ampules become contaminated, they have the potential to become a source of infection to patients.

CONTRAINDICATIONS
- Hypersensitivity to Paracetamol and other ingredients in the product
- Repeated administration is contraindicated in patients with anemia, cardiac, pulmonary, renal, or hepatic disease.

WARNING
Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible persons. Such sensitivity appears to occur more frequently in asthmatic than in non-asthmatic individuals. Paracetamol should be discontinued if hypersensitivity reactions occur.

PRECAUTIONS
Administer with caution to patients with preexisting anemia since cyanosis may not be apparent despite dangerously high blood methemoglobin concentrations.

Administration to patients with renal or hepatic impairment may result in accumulation of hepatotoxic conjugates.

INTERACTIONS WITH OTHER MEDICINES

CONCOMITANT DRUGS	EFFECTS
Anticonvulsants (e.g., phenytoin, barbiturates, carbamazepine)	Increased conversion of paracetamol to hepatotoxic metabolites; increased risk of hepatotoxicity.
Aspirin	No inhibition of antiplatelet effect of aspirin.
Isoniazid	Possible increased risk of hepatotoxicity
Phenothiazines	Possible increased risk of severe hypothermia.
Alcohol	Increased risk of paracetamol-induced hepatotoxicity.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

PREGNANCY AND LACTATION

Use in Pregnancy
Pregnancy Category B. Paracetamol crosses the placenta but the drug has been widely used as an analgesic in pregnancy and no adverse fetal effects have been recorded.

Breastfeeding Mothers
Paracetamol is distributed into breast milk but has not been detected in the urine of breastfed infants. Paracetamol is compatible with breastfeeding.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS
Paracetamol has low incidence of side effects when used within therapeutic doses. Minor gastrointestinal disturbances have been reported. Dermatologic reactions like pruritic maculopapular rash and urticaria have been reported. Other sensitivity reactions including laryngeal edema, angioedema and anaphylactoid reactions may occur rarely.

Hepatotoxicity can occur after ingestion of a single toxic dose or multiple excessive doses of paracetamol. Substantial elevations in alanine aminotransferase (ALT) occurred after receiving paracetamol in a dosage of 4g daily for two weeks.

Paracetamol very rarely aggravates bronchospasm in patients who are sensitive to aspirin and other non-steroidal anti-inflammatory drugs. Although paracetamol does not normally produce methemoglobinemia or hemolysis even after overdosage or in patients with glucose-6-phosphate dehydrogenase deficiency, there have been isolated reports of these complications.

Prolonged administration of large doses of paracetamol may lead to thrombocytopenia, leukopenia, agranulocytosis, and pancytopenia. Physical dependence does not develop even with prolonged use.

OVERDOSAGE AND MANAGEMENT
Paracetamol in massive overdosage may cause hepatic toxicity in some patients. In adults and children older than 12 years, 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 less than 12 years old, an acute overdosage with a paracetamol dose of less than 150 mg/kg body weight has not been associated with hepatic toxicity. 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 after ingestion. In adults and children over 12 years, any individual presenting with an unknown amount of paracetamol ingested or with a questionable or unreliable history about the time of ingestion should have a plasma paracetamol level drawn and be treated with N-acetylcysteine. Do not await results of assays for plasma paracetamol levels before initiating treatment with N-acetylcysteine. A plasma paracetamol assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

Serious toxicity or fatalities have been extremely infrequent following acute paracetamol overdose in young children, possibly because of differences in the way they metabolize paracetamol. In children, the maximum potential amount ingested can be more easily estimated. If more than 150 mg/kg or an unknown amount of paracetamol was ingested, obtain a plasma paracetamol level as soon as possible, but not sooner than four hours following ingestion. If an assay cannot be obtained and the estimated paracetamol ingestion exceeds 150 mg/kg, dosing with N-acetylcysteine should be initiated and continued for a full course of therapy.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.

AVAILABILITY
Paracetamol (Naprex®) 150 mg/mL Solution for Injection (IM/IV) (300 mg/2 mL Injection) in box of 10 ampules (in 2 mL amber ampule).

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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