

Stability Note: See individual product literature for detailed temperature information.

Injection: Store intact vials at room temperature of 20°C to 25°C (68°F to 77°F); do not refrigerate or freeze. Use within 6 hours of opening vial or transferring to another container. Incompatible with chlorpromazine and diazepam.

Oral formulations: Store at controlled room temperature. Suppositories: Store at <27°C (80°F). Do not freeze.

Mechanism of Action Although not fully elucidated, believed to inhibit the synthesis of prostaglandins in the CNS and peripherally block pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center

Pharmacodynamics

Onset of action:

Oral: <1 hour

I.V.: Analgesia: 5-10 minutes; Antipyretic: Within 30 minutes

Peak effect: I.V.: Analgesia: 1 hour

Duration:

I.V., Oral: Analgesia: 4-6 hours

I.V.: Antipyretic: ≥6 hours

Pharmacokinetics (Adult data unless noted) Note: With the exception of half-life (see below), the pharmacokinetic profile in pediatric patients (0-18 years) is similar to adult patients.

Absorption: Primarily absorbed in small intestine (rate of absorption dependent upon gastric emptying); minimal absorption from stomach; varies by dosage form

Distribution: ~1 L/kg at therapeutic doses

Protein binding: 10% to 25% at therapeutic concentrations; 8% to 43% at toxic concentrations

Metabolism: At normal therapeutic dosages, primarily hepatic metabolism to sulfate and glucuronide conjugates, while a small amount is metabolized by CYP2E1 to a highly reactive intermediate N-acetyl-p-benzoquinone imine (NAPQI), which is conjugated rapidly with glutathione and inactivated to nontoxic cysteine and mercapturic acid conjugates. At toxic doses (as little as 4000 mg in a single day), glutathione conjugation becomes insufficient to meet the metabolic demand causing an increase in NAPQI concentrations, which may cause hepatic cell necrosis. Oral administration is subject to first-pass metabolism.

Half-life:

Neonates: ~7 hours

Infants: ~4 hours

Children and Adolescents: ~3 hours

Adults: ~2 hours; severe renal insufficiency (Cl_{cr} <30 mL/minute): 2-5.3 hours

Time to peak serum concentration:

Oral: Immediate release: 10-60 minutes (may be delayed in acute overdoses)

I.V.: 15 minutes

Elimination: Urine (<5% unchanged; 60% to 80% as glucuronide metabolites; 20% to 30% as sulfate metabolites; ~8% cysteine and mercapturic acid metabolites)

Dosing: Neonatal

I.V.: Limited data available; dose not established: Manufacturer's neonatal (PMA not specified) pharmacokinetic data suggest a maximum single dose: 7.5 mg/kg; maximum total daily dose: 37.5 mg/kg/day. **Note:** Some experts do not recommend the use of I.V. acetaminophen in premature neonates <32 weeks PMA until pharmacokinetic and pharmacodynamic studies have been conducted in this age group (van den Anker, 2011). Postmenstrual age (PMA) is the sum of GA (weeks) and PNA (weeks) (AAP, 2004).

Loading dose (Allegaert, 2007; Bartocci, 2007): 20 mg/kg/dose

Maintenance dose (Allegaert, 2007; Allegaert, 2011; Bartocci, 2007):

PMA 28-32 weeks: 10 mg/kg/dose every 12 hours; some suggest 7.5 mg/kg/dose every 8 hours; maximum daily dose: 22.5 mg/kg/day

PMA 33-36 weeks: 10 mg/kg/dose every 8 hours; some suggest 7.5-10 mg/kg/dose every 6 hours; maximum daily dose: 40 mg/kg/day

PMA ≥37 weeks: 10 mg/kg/dose every 6 hours; maximum daily dose: 40 mg/kg/day

Oral (Anand, 2001; Anand, 2002):

GA 28-32 weeks: 10-12 mg/kg/dose every 6-8 hours; maximum daily dose: 40 mg/kg/day

GA 33-37 weeks or term neonates <10 days: 10-15 mg/kg/dose every 6 hours; maximum daily dose: 60 mg/kg/day

Term neonates ≥10 days: 10-15 mg/kg/dose every 4-6 hours; maximum daily dose: 90 mg/kg/day

Rectal (Anand, 2001; Anand, 2002):

GA 28-32 weeks: 20 mg/kg/dose every 12 hours; maximum daily dose: 40 mg/kg/day

GA 33-37 weeks or term neonates <10 days: Loading dose: 30 mg/kg; then 15 mg/kg/dose every 8 hours; maximum daily dose: 60 mg/kg/day

Term infants ≥10 days: Loading dose: 30 mg/kg; then 20 mg/kg/dose every 6-8 hours; maximum daily dose: 90 mg/kg/day

Dosing: Usual

Infants and Children:

I.V.:

Infants and Children <2 years: 7.5-15 mg/kg/dose every 6 hours; maximum total daily dose: 60 mg/kg/day (Wilson-Smith, 2009); manufacturer's pharmacokinetic data suggest a maximum single dose: 10 mg/kg;

maximum total daily dose: 50 mg/kg/day

Children 2-12 years: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours; maximum single dose: 15 mg/kg; maximum total daily dose: 75 mg/kg/day

not to exceed 3750 mg/day

Oral: 10-15 mg/kg/dose every 4-6 hours as needed; do not exceed 5 doses in 24 hours; alternatively, the following manufacturer recommended doses may be used. See table.

Acetaminophen Dosing (Oral)¹

Weight (kg)	Weight (lbs)	Age	Dosage (mg)
2.7-5.3	6-11	0-3 mo	40
5.4-8.1	12-17	4-11 mo	80
8.2-10.8	18-23	1-2 y	120
10.9-16.3	24-35	2-3 y	160
16.4-21.7	36-47	4-5 y	240
21.8-27.2	48-59	6-8 y	320
27.3-32.6	60-71	9-10 y	400
32.7-43.2	72-95	11 y	480

¹Manufacturer's recommendations; use of weight to select dose is preferred; if weight is not available, then use age. Manufacturer's recommendations are based on weight in pounds (OTC labeling); weight in kg listed here is derived from pounds and rounded; kg weight listed also is adjusted to allow for continuous weight ranges in kg. OTC labeling instructs consumer to consult with physician for dosing instructions in children under 2 years of age.

Rectal: 10-20 mg/kg/dose every 4-6 hours as needed.

Note: Although the perioperative use of high-dose rectal acetaminophen (eg, 25-45 mg/kg/dose) has been investigated in several studies, its routine use remains controversial; optimal doses and dosing frequency to ensure efficacy and safety have not yet been established; further studies are needed (Buck, 2001).