Thiazide-Like Diuretics; Tipranavir; Tolperisone; Vitamin E (Systemic); Voriconazole; Zaltoprofen

Decreased Effect

Ibuprofen may decrease the levels/effects of: ACE Inhibitors; Aliskiren; Angiotensin II Receptor Blockers; Beta-Blockers; Eplerenone; HydrALAZINE; Imatinib; Loop Diuretics; Potassium-Sparing Diuretics; Prostaglandins (Ophthalmic); Salicylates; Selective Serotonin Reuptake Inhibitors; Thiazide and Thiazide-Like Diuretics

The levels/effects of Ibuprofen may be decreased by: Bile Acid Sequestrants; Salicylates

Food Interactions Ibuprofen peak serum levels may be decreased if taken with food. Management: Administer with food.

Storage/Stability

Ibuprofen injection (Caldolor): Store intact vials at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Must be diluted prior to use. Diluted solutions are stable in D5W, LR, or NS for 24 hours at 20°C to 25°C (68°F to 77°F).

Ibuprofen lysine injection (NeoProfen): Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Protect from light. Store vials in carton until use. After first withdrawal from vial, discard remaining solution (preservative free). Following dilution in D5W or NS, use within 30 minutes.

Suspension: Store at 15°C to 30°C (59°F to 86°F).

Tablet: Store at 20°C to 25°C (68°F to 77°F).

Mechanism of Action Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which results in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Other proposed mechanisms not fully elucidated (and possibly contributing to the anti-inflammatory effect to varying degrees), include inhibiting chemotaxis, altering lymphocyte activity, inhibiting neutrophil aggregation/activation, and decreasing proinflammatory cytokine levels.

Pharmacodynamics/Kinetics (Adult data unless noted)

Onset of action: Oral: Analgesic: Within 30 to 60 minutes (Davies 1998; Mehlisch 2013); Antipyretic: Single oral dose 8 mg/kg (Kauffman 1992): Infants ≤1 year: 69 ± 22 minutes; Children ≥6 years: Single oral dose 8 mg/kg (Kauffman 1992): 109 ± 64 minutes; Adults: <1 hour (Sullivan 2011)

Maximum effect: Antipyretic: 2 to 4 hours

Duration: Oral: Antipyretic: 6 to 8 hours (Sullivan 2011)

Absorption: Oral: Rapid (85%)

Distribution: V_d:

Oral: Febrile children <11 years: 0.2 L/kg; Adults: 0.12 L/kg

IV: Ibuprofen (Caldolor):

Pediatric patients 6 months to <2 years: 0.31 L/kg

Pediatric patients 2 to 16 years: 0.23 L/kg

IV: Ibuprofen lysine: Premature neonates, GA <32 weeks: Variable results observed: 0.32 L/kg, others have reported: a central compartment Vd that decreases with increasing PNA and ductal closure (Van Overmeire, 2001) and a V_d, apparent: 0.062 L/kg in 21 premature neonates (GA <32 weeks, PNA: <1 day) (Aranda 1997); a 2-compartment open model was observed

Protein binding: >99%; Premature infants: ~95% (Aranda 1997)

Bioavailability: 80%

Metabolism: Hepatic via oxidation; **Note:** Ibuprofen is a racemic mixture of R and S isomers; the R isomer (thought to be inactive) is slowly and incompletely (~60%) converted to the S isomer (active) in adults; the amount of conversion in children is not known, but it is thought to be similar to adults; a study in preterm neonates estimated the conversion to be 61% after prophylactic ibuprofen use and 86% after curative treatment (Gregoire 2004).

Half-life elimination: IV:

Ibuprofen (Caldor):

Pediatric patients: 6 months to <2 years: 1.8 hours; 2 to 16 years: ~1.5 hours

Adults: 2.22 to 2.44 hours

Ibuprofen lysine (Neoprofen):

Premature neonates, GA <32 weeks: Reported data highly variable

R-enantiomer: 10 hours; S-enantiomer: 25.5 hours (Gregoire 2004)

Age-based observations:

PNA <1 day: 30.5 ± 4.2 hours (Aranda 1997)

PNA 3 days: 43.1 ± 26.1 hours (Van Overmeire 2001)

PNA 5 days: 26.8 ± 23.6 hours (Van Overmeire 2001)

Half-life elimination: Oral:

Children 3 months to 10 years: Oral suspension: 1.6 ± 0.7 hours (Kauffman 1992)

Adults: ~2 hours; End-stage renal disease: Unchanged (Aronoff 2007)

Time to peak: Tablets: 1 to 2 hours; Suspension: 1 hour

Children with cystic fibrosis (Scott 1999):

Suspension (n=22): 0.74 ± 0.43 hours (median: 30 minutes)

Chewable tablet (n=4): 1.5 ± 0.58 hours (median: 1.5 hours)

Tablet (n=12): 1.33 ± 0.95 hours (median: 1 hour)

Excretion: Urine (primarily as metabolites (45% to 80%); ~1% as unchanged drug and 14% as conjugated); some feces

Dosing: Neonatal Note: Oral liquid products are available in two concentrations (ie, concentrated infant drops: 50 mg/1.25 mL and suspension: 100 mg/5 mL); precautions should be taken to verify and avoid confusion between the different concentrations; dose should be clearly presented as "mg".

PDA closure: Note: Use birth weight to calculate all doses; monitor urine output; a decrease in urine output may require dose adjustment or holding of therapy.

IV:

Manufacturer's labeling: Ibuprofen lysine (NeoProfen): GA ≤32 weeks weighing 500 to 1,500 g at birth: Initial dose: 10 mg/kg, followed by two doses of 5 mg/kg/dose at 24 and 48 hours after the initial dose. A second course of treatment, alternative pharmacologic therapy, or surgery may be needed if the ductus arteriosus fails to close or reopens following the initial course of therapy.

Alternate dosing: Ibuprofen lysine: Reported dosing approach variable (standard or high-dose therapy):

Standard-dose therapy: Limited data available: GA >32 weeks: Initial dose: 10 mg/kg, followed by two doses of 5 mg/kg/dose administered at 24 hour intervals (Hirt 2008; Meißner 2012)

High-dose therapy: Limited data available: GA 24 to <40 weeks: Initial dose: 20 mg/kg, followed by two doses of 10 mg/kg/dose administered at 24-hour intervals has been evaluated in a total of 58 neonates in two studies (GA: 24 to 39 weeks, PNA ≤5 days for majority of patients). In comparison to the standard dose, these studies found a higher rate of PDA closure using high dose therapy without an increase in adverse effects (Dani 2012; Meißner 2012). Pharmacokinetic data suggest that clearance increases with postnatal age; therefore, doses at the higher end of the dosage range may be necessary in older neonates (Hirt 2008; Van Overmeire 2001).

Oral suspension: Limited data available: GA <34 weeks weighing <1500 g at birth: Initial dose: 10 mg/kg, followed by two doses of 5 mg/kg/dose at 24 and 48 hours after the initial dose; doses were administered undiluted through a feeding tube and immediately followed with a flush (~1 mL) of distilled water; this dosing regimen has been used in several trials and has been shown to be safe and as effective as IV ibuprofen and IV indomethacin (Erdeve 2012; Heyman 2003; Lee 2012); in one retrospective study, oral ibuprofen (n=52) was associated with lower rates of elevated serum creatinine compared to IV indomethacin (n=88) (Lee 2012).

Dosing adjustment in renal impairment: IV: Ibuprofen lysine (Neoprofen): If anuria or marked oliguria (urinary output <0.6 mL/kg/hour) is evident at the scheduled time of the second or third dose, hold dose until renal function returns to normal. Use is contraindicated in preterm infants with significant renal impairment.

Dosing: Usual Note: To reduce the risk of adverse cardiovascular and GI effects, use the lowest effective dose for the shortest period of time to achieve treatment goals:

Pediatric: **Note:** Oral liquid products are available in two concentrations (ie, concentrated infant drops: 50 mg/1.25 mL and suspension: 100 mg/5 mL); precautions should be taken to verify and avoid confusion between the different concentrations; dose should be clearly presented as "mg".

Analgesic:

IV: Ibuprofen injection (Caldolor): **Note:** Patients should be well hydrated prior to administration.

Infants 6 months to Children <12 years: 10 mg/kg/dose (maximum dose: 400 mg/dose) every 4 to 6 hours as needed; maximum daily dose: 40 mg/kg/**day** or 2,400 mg/**day**, whichever is less

Children and Adolescents 12 to 17 years: 400 mg every 4 to 6 hours as needed; maximum daily dose: 2,400 mg/**day**

Oral:

Weight-directed dosing: Infants and Children <50 kg: Limited data available in infants <6 months: 4 to 10 mg/kg/dose every 6 to 8 hours; maximum single dose: 400 mg; maximum daily dose: 40 mg/kg/**day** (APS 2008; Berde 1990; Berde 2002; Kliegman 2011)

Fixed dosing:

Infants and Children 6 months to 11 years: See table based upon manufacturer's labeling; use of weight to select dose is preferred; if weight is not available, then use age; doses may be repeated every 6 to 8 hours; maximum: 4 doses/day; treatment of sore throat for >2 days or use in infants and children <3 years of age with sore throat is not recommended, unless directed by health care provider.

Ibuprofen Dosing

Weight (preferred)[A]		Age	Dosage (mg)
kg	lbs		
5.4 to 8.1	12 to 17	6 to 11 months	50
8.2 to 10.8	18 to 23	12 to 23 months	75
10.9 to 16.3	24 to 35	2 to 3 years	100
16.4 to 21.7	36 to 47	4 to 5 years	150
21.8 to 27.2	48 to 59	6 to 8 years	200
27.3 to 32.6	60 to 71	9 to 10 years	250
32.7 to 43.2	72 to 95	11 years	300

[A]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.

Children ≥12 years and Adolescents: Oral: 200 mg every 4 to 6 hours as needed; if pain does not respond may increase to 400 mg; maximum daily dose: 1,200 mg/**day**; treatment of pain for >10 days is not recommended, unless directed by health care provider

Antipyretic:

IV: Ibuprofen injection (Caldolor): **Note:** Patients should be well hydrated prior to administration.

Infants 6 months to Children <12 years: 10 mg/kg/dose (maximum dose: 400 mg/dose) every 4 to 6 hours as needed; maximum daily dose: 40 mg/kg/**day** or 2,400 mg/**day**, whichever is less

Children and Adolescents 12 to 17 years: 400 mg every 4 to 6 hours as needed; maximum daily dose: 2,400 mg/**day**

Oral:

Weight-directed dosing: Infants ≥6 months, Children, and Adolescents: 5 to 10 mg/kg/dose every 6 to 8 hours; maximum single dose: 400 mg; maximum daily dose: 40 mg/kg/**day** up to 1,200 mg, unless directed by physician; under physician supervision daily doses ≤2,400 mg may be used (Kliegman 2011; Litalien 2001; Sullivan 2011)

Fixed dosing:

Infants and Children 6 months to 11 years: Oral: See table based upon manufacturer's labeling; use of weight to select dose is preferred; if weight is not available, then use age; doses may be repeated every 6 to 8 hours; maximum: 4 doses/day; treatment for >3 days is not recommended unless directed by health care provider

Weight (preferred)[A]		Age	Dosage (mg)
kg	lbs		
5.4 to 8.1	12 to 17	6 to 11 months	50
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16.4 to 21.7	36 to 47	4 to 5 years	150
21.8 to 27.2	48 to 59	6 to 8 years	200
27.3 to 32.6	60 to 71	9 to 10 years	250
32.7 to 43.2	72 to 95	11 years	300

[A]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.

Cystic fibrosis, mild disease (to slow lung disease progression): Limited data available: Children and Adolescents 6 to 17 years with FEV_1 >60% predicted (Mogayzel 2013): Oral: Initial: 20 to 30 mg/kg/dose twice daily; titrate to achieve peak plasma concentrations of 50 to 100 mcg/mL; should not eat or take pancreatic enzymes for 2 hours after the ibuprofen dose. Dosing based on a study of 41 patients (ages: 5 to 39 years); mean required dose: ~25 mg/kg/dose twice daily, reported range: 16.2 to 31.6 mg/kg/dose every 12 hours required to achieve target concentration; results showed that chronic ibuprofen use (over 4 years) slowed the rate of decline in FEV_1; patients 5 to 13 years old with mild lung disease were observed to have greatest benefit; (Konstan 1995). A follow up observational study (n=1,365; ages: 6 to 17 years) under noncontrolled conditions (real world) showed significant improvement in the rate of decline of lung disease progression with chronic ibuprofen therapy (Konstan 2007). **Note:** Timing of blood sampling post-dose is based on dosage form: Oral suspension: Obtain blood samples at 30, 45, and 60 minutes postdose; tablets: Obtain blood samples at 1, 2, and 3 hours postdose (Litalien 2001; Scott 1999).

Juvenile idiopathic arthritis (JIA): Children and Adolescents: Usual range: 30 to 40 mg/kg/**day** in 3 to 4 divided doses; start at lower end of dosing range and titrate; patients with milder disease may be treated with 20 mg/kg/**day**; patients with more severe disease may require up to 50 mg/kg/**day**; maximum single dose: 800 mg; maximum daily dose: 2,400 mg/**day** (Giannini 1990; Kliegman 2011; Litalien 2001)

Adult:

Analgesia/pain/dysmenorrhea: Oral: 400 mg/dose every 4 to 6 hours

Analgesic: IV (Caldolor): 400 to 800 mg every 6 hours as needed; maximum daily dose: 3,200 mg/**day**. **Note:** Patients should be well hydrated prior to administration.

Antipyretic: IV (Caldolor): Initial: 400 mg, then 400 mg every 4 to 6 hours or 100 to 200 mg every 4 hours as needed; maximum daily dose: 3,200 mg/**day**. **Note:** Patients should be well hydrated prior to administration.

Osteoarthritis, rheumatoid arthritis: Oral: 400 to 800 mg 3 to 4 times daily (maximum: 3,200 mg/day)

OTC labeling:

Analgesia/Antipyretic: Oral: 200 mg every 4 to 6 hours as needed; if no relief may increase to 400 mg every 4 to 6 hours as needed; maximum daily dose: 1,200 mg/24 hours; treatment for >10 days as an analgesic or >3 days as an antipyretic is not recommended unless directed by health care provider

Migraine: Oral: 400 mg at onset of symptoms; maximum daily dose: 400 mg/24 hours unless directed by health care provider

Dosing adjustment in renal impairment: Oral, IV: There are no dosage adjustments provided in the manufacturer's labeling; avoid use in advanced disease.

KDIGO 2012 guidelines provide the following recommendations for NSAIDs: Infants, Children, Adolescents, and Adults:

eGFR 30 to <60 mL/minute/1.73 m^2: Avoid use in patients with intercurrent disease that increases risk of acute kidney injury

eGFR <30 mL/minute/1.73 m^2: Avoid use

Dosing adjustment in hepatic impairment: There are no dosage adjustments provided in the manufacturer's labeling; use caution and discontinue if hepatic function worsens.

Preparation for Administration IV:

Ibuprofen injection (Caldolor): Must be diluted prior to use. Dilute with D5W, NS or LR to a final concentration ≤4 mg/mL.

Ibuprofen lysine injection (NeoProfen): Dilute with dextrose or saline to an appropriate volume.

Administration

Oral: Administer with food or milk to decrease GI upset; shake suspension well before use

IV:

Ibuprofen injection (Caldolor): For IV administration only; in pediatric patients, infuse over at least 10 minutes; in adults, infuse dose over at least 30 minutes

Ibuprofen lysine injection (NeoProfen): For IV administration only; administration via umbilical arterial line has not been evaluated. Infuse over 15 minutes through IV port closest to insertion site. Avoid extravasation. Do not administer simultaneously via same line with TPN. If needed, interrupt TPN for 15 minutes prior to and after ibuprofen administration, keeping line open with dextrose or saline.

Monitoring Parameters CBC, serum electrolytes, occult blood loss, liver enzymes; urine output, serum BUN, and creatinine in patients receiving IV ibuprofen, concurrent diuretics, those with decreased renal function, or in patients on chronic therapy. Monitor preterm neonates for signs of bleeding and infection; serum electrolytes, glucose, calcium and bilirubin; vital signs; monitor IV site for signs of extravasation. Patients receiving long-term