Topiramate
Newborn Use Only

2017

Alert	The safety and efficacy of topiramate therapy in neonatal seizures is unclear. Consult a paediatric neurologist for further advice on dose recommendations. Suspension: Shake well before using.
Indication	Treatment of neonatal seizures refractory to other antiepileptic drugs.
Action	Topiramate acts by reducing excitatory neurotransmission (glutamatergic synapse) preventing depolarisation by inhibiting voltage-gated sodium channels. On the postsynaptic terminal, topiramate is an antagonist at the ionotropic glutamate receptors (AMPA and kainate).
Drug Type	Anticonvulsant.
Trade Name	APO Topiramate, Epiramax, Topamax, Tamate,
Presentation	Topiramate 5 mg/mL in SyrSpend SF PH4 (suspension). Topiramate 6 mg/mL in Oraplus/Orasweet or Orablend (suspension).
Dosage / Interval	**Dose:** Begin at 1 to 3 mg/kg/day as a single (nightly) dose for the first week. The dosage should then be increased by 1 to 3 mg/kg/day at weekly or longer intervals to the recommended total daily dose of 5 to 10 mg/kg/day in 1–2 divided doses. Daily doses over 10 mg/kg in infants over 1 month age have been studied and were generally well tolerated. The daily dosage should be given as two divided doses.
Route	Oral
Preparation/Dilution	**Oral** Give undiluted.
Administration	Oral: May be given with or without feed. **Shake well before using.**
Monitoring	Monitor side effects clinically (see adverse reactions). Monitor renal function, serum bicarbonate and for metabolic acidosis at baseline and periodically during treatment. Ammonia concentration in any infant with lethargy or vomiting.
Contraindications	Hypersensitivity to any component of the product.
Precautions	Antiepileptic drugs, including topiramate, should be gradually withdrawn to minimise the potential for seizures or increased seizure frequency. May be associated with metabolic acidosis and heat intolerance – see monitoring. Use with caution in renal and hepatic impairment.
Drug Interactions	Concurrent use of topiramate with several antiepileptic drugs [valproic acid; phenytoin; carbamazepine; phenobarbital] may result in decreased topiramate concentrations. Concurrent use with valproic acid may increase risk of hyperammonaemia, encephalopathy and hypothermia. Concurrent use with CNS depressants [opioids] may increase risk of CNS depression. Concurrent use with hydrochlorothiazide may increase topiramate concentration. Concurrent use with diuretics causing hypercalciuria may increase risk of nephrolithiasis.
Adverse Reactions	There is currently insufficient evidence on the safety of topiramate in neonates. From the few data available, it appears well-tolerated. Common [reported in all populations]: Dermatological: Flushing (Paediatrics 5%); Endocrine/metabolic: Serum bicarbonate abnormal (25% to 67%); Gastrointestinal: Loss of appetite (10% to 24%), weight decreased (4% to 21%); Neurological: Confusion (3% to 11%), dizziness (4% to 25%), impaired cognition (2% to 7%), impaired psychomotor performance (2% to 13%), memory impairment (3% to 12%), paraesthesia (1% to 51%), reduced concentration span (2% to 10%), somnolence (6% to 29%); Psychiatric: Feeling nervous (4% to 16%), mood disorder (4% to 11%); fatigue (6% to 16%); Other: Fever (1% to 12%). Serious [reported in all populations]: Dermatological: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis; Endocrine/metabolic: Hyperammonaemia (adolescents, 26%), hypohidrosis, increased body temperature, metabolic acidosis; Hepatic: Liver failure; Neurological: Drug-induced encephalopathy; Ophthalmic: Glaucoma, myopia, visual field defect (epilepsy, 0.1% to 1%); Renal: Nephrolithiasis (adults, 1% to 3%).
Compatibility	No information.
Incompatibility	No information.

Stability	Stable at 2−8°C for 90 days.
Storage	Tight, light-resistant container with sufficient head space for shaking. Store 2–8°C.
Special Comments	The goal is to achieve clinical control of seizures. There is a paucity of evidence on target serum concentrations in neonates. Therapeutic concentrations are not routinely measured but may be useful to optimise dose and interval. Plasma topiramate concentration reference range 5–20 microgram/mL [1].
Evidence summary	**Treatment of seizures in term infants:** There is a paucity of information about the safety, efficacy or pharmacokinetics in a critically ill new-born population. Responses to topiramate 6 mg/kg/day [2] and 10 mg/kg/day [3] have been reported in newborn infants with seizures refractory to other drugs. (LOE IV GOR D] **Neuroprotection in term/near term infants with hypoxic ischaemic encephalopathy (HIE):** Topiramate is hypothesised to have synergistic neuroprotective effects in neonates. It reduces brain injury in animal models of HIE [4] and its use has been piloted in infants with HIE undergoing hypothermia treatment [1, 5] with results of a clinical trial awaited [6]. There are insufficient data to recommend use of topiramate in infants with HIE undergoing hypothermia. [LOE IV GOR D] **Safety:** There is currently insufficient evidence on the safety of topiramate in neonates [4]. From the few data available it appears well-tolerated. [LOE IV GOR D] **Pharmacokinetics:** In neonates with HIE undergoing hypothermia, topiramate 5 mg/kg/daily produced plasma topiramate concentrations within the reference range (5–20 microgram/mL). Reported half-life ± SD was 35.6 ± 19.3 hours; fraction unbound ~85%; clearance 0.0156 ± 0.0048 L/hour/kg; and volume of distribution, Vd 0.6–1 L/kg [1, 7]. In adults, after oral administration, topiramate is well absorbed from the gastrointestinal tract and shows linear pharmacokinetics. Renal excretion (40–70% of the dose) and CYP-mediated oxidation to several inactive metabolites [8].
References	1. Filippi L, la Marca G, Fiorini P, Poggi C, Cavallaro G, Malvagia S, Pellegrini-Giampietro DE, Guerrini R. Topiramate concentrations in neonates treated with prolonged whole body hypothermia for hypoxic ischemic encephalopathy. Epilepsia. 2009;50:2355-61. 2. Kundak AA, Okumus N, Dilli D, Erol S, Zenciroglu A. Topiramate use in the neonatal period. Pediatr Neurol. 2012;46:410; author reply 3. Glass HC, Poulin C, Shevell MI. Topiramate for the treatment of neonatal seizures. Pediatric neurology. 2011;44:439-42. 4. Donovan MD, Griffin BT, Kharoshankaya L, Cryan JF, Boylan GB. Pharmacotherapy for Neonatal Seizures: Current Knowledge and Future Perspectives. Drugs. 2016;76:647-61. 5. Filippi L, Poggi C, la Marca G, Furlanetto S, Fiorini P, Cavallaro G, Plantulli A, Donzelli G, Guerrini R. Oral topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia: a safety study. J Pediatr. 2010;157:361-6. 6. Filippi L, Fiorini P, Daniotti M, Catarzi S, Savelli S, Fonda C, Bartalena L, Boldrini A, Giampietri M, Scaramuzzo R, Papoff P, Del Balzo F, Spalice A, la Marca G, Malvagia S, Della Bona ML, Donzelli G, Tinelli F, Cioni G, Pisano T, Falchi M, Guerrini R. Safety and efficacy of topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia (NeoNATI). BMC Pediatr. 2012;12:144. 7. Tulloch JK, Carr RR, Ensom MH. A systematic review of the pharmacokinetics of antiepileptic drugs in neonates with refractory seizures. J Pediatr Pharmacol Ther. 2012;17:31-44. 8. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin Pharmacokinet. 2013;52:627-45. 9. Micromedex. 2017 Truven Health Analytics Inc. http://www.micromedexsolutions.com.acs.hcn.com.au accessed 12/04/2017.

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