Topiramate
Newborn Use Only

2021

Alert	There is limited data about safety and efficacy of topiramate in neonates. Consult a paediatric neurologist for further advice on dose recommendations.
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	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.(ANMF neurologist review)[1,2]
Route	Oral
Dose adjustments	Therapeutic hypothermia: Dose modification not required.[1,2] ECMO: insufficient evidence in neonates to make recommendations. Renal impairment: Lower doses recommended.[3] Hepatic impairment: Dose modification may not be required.[3]
Preparation	Give undiluted.
Administration	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Precautions	Antiepileptic drugs, including topiramate, should be gradually withdrawn to minimise the potential for seizures or increased seizure frequency.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 (sodium valproate; phenytoin; carbamazepine; phenobarbital) may result in decreased topiramate concentrations. Concurrent use of topiramate with phenytoin may result in increased phenytoin 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	Limited evidence in neonates. Paediatric and adult data as follow: <u>Common:</u> Dermatological: Flushing; Endocrine/metabolic: Serum bicarbonate abnormal (25% to 67%); Gastrointestinal: Loss of appetite, weight loss; Neurological: somnolence (6% to 29%); fever. <u>Serious:</u> Preterm neonates: necrotising enterocolitis.[4] 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; Renal: Nephrolithiasis.
Compatibility	No information.
Incompatibility	No information.
Stability	Check with hospital pharmacy
Storage	Check with hospital pharmacy for in-house preparation.

Excipients	APO-Topiramate: Methylcellulose, croscarmellose sodium, magnesium stearate, colloidal anhydrous silica, hypromellose, hyprolose, macrogol, titanium dioxide, iron oxide yellow (CI77492) (50 mg and 100 mg only), iron oxide red (CI77491) (200 mg only). Epiramax: microcrystalline cellulose, sodium starch glycollate, pregelatinised maize starch, lactose, Aniseed flavour 84165-31, saccharin sodium, magnesium stearate, Opadry AMB OY-B-28920 White (25 mg), Opadry AMB 80W62680 Yellow (50 mg), Opadry AMB 80W62681 Yellow (100 mg) and Opadry AMB 80W64830 Pink (200 mg). Noumed topiramate: lactose monohydrate, pregelatinised maize starch, microcrystalline cellulose, sodium starch glycollate, magnesium stearate, titanium dioxide, hypromellose, macrogol 400 and polysorbate 80. In addition, Noumed Topiramate 50 mg and 200 mg tablets contain iron oxide yellow. Tamate: microcrystalline cellulose, povidone, colloidal anhydrous silica, sodium starch glycollate type A, and magnesium stearate.
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	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 at a dose of up 3 to 10 mg/kg/day have been reported in newborn infants with seizures refractory to other drugs.[4,5] (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.[6] However, a pilot randomised control trial comprising of 44 neonates did not find any short term or long term benefit of prophylactic use of topiramate in addition to hypothermia. There was a trend towards reduced epilepsy in the treatment group compared to the control group but the difference was not statistically significant (14.3 vs 30.4%; RR 0.46; p= 0.21).[2] There are insufficient data to recommend use of topiramate for neuroprotection in infants with HIE undergoing hypothermia. [LOE IV GOR D] Safety: There is currently limited evidence on the safety of topiramate in neonates.[2,6] [Donovan, Filipi 2018. From the few data available it appears well-tolerated in term or near term neonates. [LOE IV GOR D]. Filippi et al did not find any clinically significant adverse events of topiramate in 21 neonates with HIE. The group treated with topiramate had a lower heart rate at 66-72 hours compared to the control group (98-100 vs 100-112; p=0.03) and a lower base excess after rewarming (-2.6 vs -0.2; p=0.04).[2] In a cohort of 10 preterm infants with seizures of various etiologies, Courchia et reported definite or advanced necrotising enterocolitis in 4 neonates. This association necessitates cautious use of Topiramate in preterm infants.[4] 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.[1,9]. When used at 10mg/kg once a day, the average levels were around 6.5 to 7 mg/l and increased to 12-13 mg/l after the third dose. Co-treatment with Phenobarbitone reduces the levels of Topiramate.[1,2] 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.[10]
Practice points	
References	1. Filippi L, la Marca G, Fiorini P, et al. Topiramate concentrations in neonates treated with prolonged whole body hypothermia for hypoxic ischemic encephalopathy. Epilepsia. 2009; 50:2355-61. 2. Filippi L, Fiorini P, Catarzi S, et al. Safety and efficacy of topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia (NeoNATI): a feasibility study, The Journal of Maternal-Fetal & Neonatal Medicine, 31:8, 973-980, 3. Prasarn Manitpisitkul, Christopher R. et al. Pharmacokinetics of topiramate in patients with renal impairment, end-stage renal disease undergoing hemodialysis, or hepatic impairment, 4. Epilepsy Research,Volume 108, Issue 5, 2014,Pages 891-901,

5. Courchia B, Kurtom W, Pensirikul A, et al. Topiramate for Seizures in Preterm Infants and the Development of Necrotizing Enterocolitis. Pediatrics. 2018; 142(1).
6. Kundak AA, Okumus N, Dilli D, Erol S, Zenciroglu A. Topiramate use in the neonatal period. Pediatr Neurol. 2012; 46:410; author reply.
7. Glass HC, Poulin C, Shevell MI. Topiramate for the treatment of neonatal seizures. Pediatric neurology. 2011; 44:439-42.
8. Donovan MD, Griffin BT, Kharoshankaya L, Cryan JF, Boylan GB. Pharmacotherapy for Neonatal Seizures: Current Knowledge and Future Perspectives. Drugs. 2016; 76:647-61.
9. 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.
10. Filippi L, Fiorini P, Daniotti M, et al. Safety and efficacy of topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia (NeoNATI). BMC Pediatr. 2012; 12:144.
11. 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.
12. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin Pharmacokinet. 2013; 52:627-45.
13. Micromedex. 2017 Truven Health Analytics Inc. http://www.micromedexsolutions.com.acs.hcn.com.au accessed 12/04/2017.

VERSION	DATE
Original 1.0	22/08/2017
Current 2.0	4/11/2021
REVIEW	4/11/2026

Authors Contribution

Original author/s	Nilkant Phad, Srinivas Bolisetty
Evidence review	Nilkant Phad
Expert review	Richard Webster
Nursing review	Kirsty Minter, Eszter Jozsa, Priya Govindaswamy
Pharmacy review	Simarjit Kaur, Joanne Malloy
ANMF group contribution	Bhavesh Mehta, John Sinn, Thao Tran, Michelle Jenkins, Cindy Chen, Mohammad Irfan Azeem, Helen Huynh, Hannah Bell
Final editing of the original	Thao Tran
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty