LevETIRAcetam

Newborn use only

2021

Alert	
Indication	Treatment of neonatal seizures
Action	The exact mechanism of action is unclear. It appears to act by modulation of synaptic neurotransmitter release (GABA, glutamic acid) through binding to the synaptic vesicle glycoprotein 2A and by effects on calcium entry and release pathways in the brain.
Drug type	Anticonvulsant
Trade name	IV: Hospira Levetiracetam, Levetiracetam APOTEX, Levetiracetam Sandoz, Levetiracetam-AFT Oral: Keppra, Kerron, Levetiracetam-AFT, APO-Levetiracetam, Levetiracetam GH
Presentation	500 mg/5 mL vial 100 mg/mL oral solution
Dose	**Acute onset seizures (e.g. hypoxic ischaemic encephalopathy)** **Loading Dose –** 40 mg/kg followed by an additional 20mg/kg after 30 minutes if required.(1) **Maintenance dose –10 mg/kg/dose 8 hourly.(2)** To commence 12 hours after loading dose. Dose can be increased to 30 mg/kg/dose (maximum 60 mg/kg/day). **Add-on/Maintenance therapy for recurrent seizures** 10 mg/kg/dose 8 hourly. (1, 2) Dose can be increased to 30 mg/kg/dose (maximum 60 mg/kg/day).
Dose adjustment	Therapeutic hypothermia – No dose adjustment required.(2) ECMO – No information. Renal impairment – dosage adjustment may be necessary. Discuss with paediatric neurologist. Hepatic impairment – No dose adjustment is required.
Maximum dose	Loading: 60 mg/kg/dose. Maintenance: 60 mg/kg/day.(3)
Total cumulative dose	
Route	IV or Oral.
Preparation	**IV** Draw up 3 mL (300 mg) and add 17 mL of sodium chloride 0.9% or glucose 5% to make a final volume of 20 mL with a concentration of 15 mg/mL.(17,18) **Oral** Give undiluted. If volume is too small, take 1 mL (100 mg) and add 9 mL of water for injection to make a final volume of 10 mL with a concentration of 10 mg/mL.
Administration	IV infusion: Infuse over 15 minutes.(1,2) Oral: May be given with or without feed (although feed delays the absorption of levetiracetam – this is not a problem if the infant is on maintenance doses). May be given at the same time as other medications.
Monitoring	Seizure frequency, duration and severity. Watch for hypotension, respiratory suppression, sedation. Renal function. Therapeutic drug monitoring – Routine monitoring of **trough** serum concentrations is not necessary. Monitoring may be considered in neonates with seizures resistant to high dose therapy or exhibiting adverse reactions. The reference range for serum levetiracetam concentrations has not been well established and may vary from 6-20 microgram/mL.(2)
Contraindications	Hypersensitivity to levetiracetam or any of the ingredients.
Precautions	Do not stop levetiracetam therapy abruptly in infants on prolonged therapy. Use with caution in renal impairment. Preterm neonates - Although similar dosing has been used, there are minimal pharmacokinetic data in this population.
Drug interactions	Increased clearance by 30% was suggested with co-administration of phenobarbital and phenytoin in children and adults and similar association may explain increased clearance in neonates.(2, 4)

Adverse reactions	Well tolerated drug. Sedation and irritability. Rare (noted in children and adults, not in neonates so far): thrombocytopenia, leukopenia, neutropenia, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hepatitis, hepatic failure, weight loss, pancreatitis.
Compatibility	Fluids (15): Glucose 5% (10% not tested), sodium chloride 0.9%. Y-site (15,16): No information available.
Incompatibility	Fluids: No information. Y-site (15,16): No information.
Stability	IV diluted solution – Sandoz, AFT: stable for 24 hours at 2−8°C or for 6 hours at 25°C. Hospira, Apotex: stable for 24 hours at 2−8°C. Oral solution: Once opened, discard after 7 months.
Storage	IV and Oral: Store below 25°C.
Excipients	Oral: sodium citrate or sodium citrate dihydrate, citric acid monohydrate, methyl hydroxybenzoate, propyl hydroxybenzoate, ammonium glycyrrhizate, glycerol, maltitol solution, acesulfame potassium, grape or grapefruit flavour and purified water. Kerron: does not contain ammonium glycyrrhizate but also contains propylene glycol and mafco magnasweet 110. IV: Apotex, Sandoz, AFT: sodium acetate trihydrate, sodium chloride, glacial acetic acid and water for injection. Hospira: sodium acetate trihydrate, sodium chloride, glacial acetic acid, water for injection and nitrogen.
Special comments	In children, oral bioavailability is 100% and no dose adjustment necessary when changing from IV to oral or vice versa. If therapy is to be stopped, levetiracetam should be withdrawn slowly in consultation with a paediatric neurologist. A general weaning regimen is 20–25% reduction per week over 4–5 weeks.(5)
Evidence	**Efficacy** **Treatment of seizures in term infants:** **Levetiracetam (LEV) versus phenobarbital as first line therapy:** A multicentre blinded phase IIb RCT (NEOLEV2 study) investigating the efficacy and safety of levetiracetam compared with phenobarbital as a first line treatment for EEG-confirmed neonatal seizures of any cause found that 80% of neonates in phenobarbital group (20 mg/kg loading followed by additional loading 20 mg/kg if required) remained seizure free for 24 hours, compared with 28% of neonates in levetiracetam (40 mg/kg loading followed by additional 20 mg/kg).(1) NEOLEV2 study is a well-designed trial with consistent dosages administered for each drug and well-defined escalation protocols. In this study, all neonates had seizures confirmed by continuous electroencephalography and validated by two independent neurophysiologists. Seizure cessation was defined clinically and electrographically and thus captured and monitored the full burden of seizures. Gowda et al, in a single centre, open labelled RCT of clinically detected neonatal seizures, Levetiracetam (20 mg/kg followed by 20 mg/kg) achieved better control than phenobarbitone (20 mg/kg followed by 10 mg/kg) for neonatal seizures when used as first-line antiepileptic drug. Seizure diagnosis in Gowda's trial was clinical, all neonates were outborn and intervention was an open label.(6) There are other retrospective and cohort studies with varied outcomes.(7) **Dose regimen for acute neonatal seizures:** Sharpe C.M. et al (2) proposed a maintenance dosing regimen of 10 mg/kg/dose 8 hourly following loading dose of 40 mg/kg to maintain trough levels above 20 mg/L during the first 3 days of treatment when seizures occur more frequently. Although the LEV dose proposed (10 mg/kg/dose 8 hourly) by Sharpe et al is higher than those indicated for the neonatal population, the risk of significant adverse effects is minimal for LEV because of its wide therapeutic index. This study included term infants during the first few days of life with relatively normal renal function for age. Given the dynamic nature of LEV clearance (CL) in our study population, preterm and older term infants or those with some renal dysfunction are likely to have different LEV CL and possibly altered dosing requirements. However, LEV has a wide safety margin. **Treatment of seizures in preterm infants:** Studies reported varied response rates to levetiracetam when used either first line or for seizures refractory to other anti-epileptic drugs. Loading doses ranged from 10–60 mg/kg/day and maintenance dose 10-30 mg/kg/day were used.(8-11) (LOE IV)

	Therapeutic hypothermia (TH): Sharpe et al. published population pharmacokinetic analysis of 18 neonates that showed that clearance increased by 90% on day 7 of life compared with day 1. Five of these infants were treated with TH. In the analysis, TH was not a significant covariate on levetiracetam clearance.(2) **Renal impairment:** The majority of the administered LEV dose is excreted unchanged by kidneys. Adult data suggests that renal impairment will decrease the clearance of LEV and, therefore, increase the half-life.(12) **Safety:** Levetiracetam use in neonates appears to be safe and well tolerated even in extreme preterm neonates.(1-3, 8-12) **Pharmacokinetics:** The half-life in neonates is longer compared to older children.(13) Peak plasma concentrations are achieved at 1.4 hours after an oral dose. Median half-life was reported to be 18.5 ± 7.1 hours on day 1 and averaged approximately 9 hours (range 3–13 hours) when assessed day 7–30. Over the first week, the CL increases into the range of older children.(13) The CL is lower in neonates and infants with renal impairment requiring monitoring of trough concentrations and dose adjustment.(13, 14) In children, the clearance was reported to be increased by 30% with co-administration of phenobarbital (phenobarbitone), carbamazepine and phenytoin.(11)
Practice points	Phenobarbital loading dose is superior to levetiracetam loading dose as the first line therapy for treatment of acute neonatal seizures.(1, 7) (LOEII, GOR B) ANMF group consensus is to adapt the dose regimen used in studies by Sharpe et al.(1, 2)
References	1. Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, Rasmussen M, et al. Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. Pediatrics. 2020;145(6). 2. Sharpe CM, Capparelli EV, Mower A, Farrell MJ, Soldin SJ, Haas RH. A seven-day study of the pharmacokinetics of intravenous levetiracetam in neonates: marked changes in pharmacokinetics occur during the first week of life. Pediatric research. 2012;72(1):43-9. 3. Mruk AL, Garlitz KL, Leung NR. Levetiracetam in neonatal seizures: a review. The Journal of Pediatric Pharmacology and Therapeutics. 2015;20(2):76-89. 4. Dahlin MG, Wide K, Ohman I. Age and comedications influence levetiracetam pharmacokinetics in children. Pediatric neurology. 2010;43(4):231-5. 5. Louis EKS, Gidal BE, Henry TR, Kaydanova Y, Krumholz A, McCabe PH, et al. Conversions between monotherapies in epilepsy: expert consensus. Epilepsy & Behavior. 2007;11(2):222-34. 6. Gowda VK, Romana A, Shivanna NH, Benakappa N, Benakappa A. Levetiracetam versus phenobarbitone in neonatal seizures—A randomized controlled trial. Indian pediatrics. 2019;56(8):643-6. 7. Giva S, Boyle MA, Gorman KM. Should levetiracetam rather than phenobarbitone be the first-line treatment for neonatal seizures? Archives of Disease in Childhood. 2021;106(3):301-3. 8. Han JY, Moon CJ, Youn YA, Sung IK, Lee IG. Efficacy of levetiracetam for neonatal seizures in preterm infants. BMC pediatrics. 2018;18(1):131. 9. Khan O, Cipriani C, Wright C, Crisp E, Kirmani B. Role of intravenous levetiracetam for acute seizure management in preterm neonates. Pediatric neurology. 2013;49(5):340-3. 10. Ramantani G, Ikonomidou C, Walter B, Rating D, Dinger J. Levetiracetam: safety and efficacy in neonatal seizures. european journal of paediatric neurology. 2011;15(1):1-7. 11. Kurtom W, Courchia B, Pensirikul A, Sosenko I, Del-Moral T. Lack of response to treatment with levetiracetam in extreme preterm infants with seizures. Journal of Perinatology. 2019;39(11):1480-4. 12. Patsalos P. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. Pharmacology & therapeutics. 2000;85(2):77-85. 13. Loiacono G, Masci M, Zaccara G, Verrotti A. The treatment of neonatal seizures: focus on Levetiracetam. The Journal of Maternal-Fetal & Neonatal Medicine. 2016;29(1):69-74. 14. Egunsola O, Choonara I, Sammons HM. Safety of levetiracetam in paediatrics: a systematic review. PloS one. 2016;11(3):e0149686. 15. Australian Injectable drugs handbook. Levetiracetam. Accessed on 20 April 2021. 16. Micromedex. Levetiracetam. Accessed on 20 April 2021.

17. Phelps SJ, Hagemann TM, Lee KR and Thompson AJ. **Paediatric Injectable Drugs**. The Teddy Bear Book. 11th. ed. Bethesda, Maryland: American Society of Health-System Pharmacists; 2018.
18. Wheless JW, Clarke D, Hovinga CA, Ellis M, Durmeier M, McGregor A, Perkins F. Rapid infusion of a loading dose of intravenous levetiracetam with minimal dilution: a safety study. J Child Neurol. 2009; 24(9): 946-51.

VERSION/NUMBER	DATE
Original	27/06/2016
Current 2.0	6/05/2021
REVIEW	6/05/2026

Authors Contribution

Original author/s	Kavitha Kothur, Srinivas Bolisetty, David Osborn
Original version evidence review	David Osborn, Srinivas Bolisetty
Current version authors	Srinivas Bolisetty, Bhavesh Mehta, Thomas Young
Expert review	Deepak Gill
Nursing Review	Eszter Jozsa, Kirsty Minter
Pharmacy Review	Thao Tran, Cindy Chen
ANMF Group contributors	Nilkant Phad, John Sinn, Jessica Mehegan, Michelle Jenkins, Helen Huynh, Simarjit Kaur
Final editing and review of the original	Ian Whyte
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty