<table>
<tr><td>Alert</td><td>The safety and efficacy of levetiracetam therapy in neonatal seizures has not been evaluated by randomised controlled trials. Consult a paediatric neurologist for further advice on dose recommendations.</td></tr>
<tr><td>Indication</td><td>Treatment of neonatal seizures.</td></tr>
<tr><td>Action</td><td>The exact mechanism of action of levetiracetam is unclear. Levetiracetam 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.</td></tr>
<tr><td>Drug Type</td><td>Anticonvulsant</td></tr>
<tr><td>Trade Name</td><td>Hospira Levetiracetam, Keppra IV, Levetiracetam IV APOTEX, Levetiracetam Juno, Levetiracetam Sandoz
Keppra Oral, Kerron Oral, Levetiracetam-AFT Oral,</td></tr>
<tr><td>Presentation</td><td>500 mg/5 mL vial
100 mg/mL oral solution</td></tr>
<tr><td>Dosage / Interval</td><td>Acute onset seizures refractory to first-line therapy (e.g. hypoxic ischaemic encephalopathy)

Loading Dose (IV or PO) – 40 mg/kg (range: 15–50 mg/kg

<table>
<tr><th colspan="2">Maintenance Dose 10 mg/kg/dose
Start 12 hours after loading dose</th></tr>
<tr><th>Postnatal Age</th><th>Interval</th></tr>
<tr><td>0–7 days</td><td>12 hourly</td></tr>
<tr><td>8+ days</td><td>8-12 hourly</td></tr>
<tr><td colspan="2">Dose can be increased to 30 mg/kg/dose (maximum 60 mg/kg/day)</td></tr>
</table>

Add-on therapy for recurrent seizures
IV or PO – 10 mg/kg/dose every 12 hours day 0-7 of life and 8-12 hourly from day 8 of life (maximum dose 60 mg/kg/day)</td></tr>
<tr><td>Route</td><td>IV and Oral</td></tr>
<tr><td>Preparation/Dilution</td><td>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. Infuse dose over 15 minutes.

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.</td></tr>
<tr><td>Administration</td><td>IV infusion: Infuse over 15 minutes.

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.</td></tr>
<tr><td>Monitoring</td><td>The goal is to achieve clinical control of seizures. Monitor side effects clinically (see adverse reactions). 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. Target trough concentration > 20 mg/L when seizure frequency is high and 10--40 mg/L subsequently titrated to seizure control. [1, 2, 16] Trough concentration may be useful to determine dosing adjustments in renal impairment. Consult paediatric neurologist for further advice.</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to levetiracetam or any of the ingredients.</td></tr>
<tr><td>Precautions</td><td>Do not stop levetiracetam therapy abruptly in infants on prolonged therapy (refer to special comments section). Use with caution in renal impairment.</td></tr>
</table>

	Although similar dosing has been used in premature infants, there are minimal pharmacokinetic data in this population.
Drug Interactions	Clearance may be increased by 30% with co-administration of phenobarbital (phenobarbitone), carbamazepine and phenytoin.
Adverse Reactions	Adverse reactions are very rare. Sedation and irritability have been reported in neonates. In children, commonly reported problems include behavioural problems and somnolence, loss of appetite, vomiting, dizziness, rash and insomnia. These are more common with polytherapy. [3] Other rare adverse effects that have been reported in older children and adults (but not observed in neonates so far): thrombocytopenia, leukopenia, neutropenia, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hepatitis, hepatic failure, weight loss, pancreatitis.
Compatibility	Fluids: Glucose 5% (10% not tested), sodium chloride 0.9%. Y-site: No information available.
Incompatibility	Fluids: No information available. Y-site: Amino acid and lipid solutions.
Stability	Diluted solution: Stable for 24 hours at 2–8°C or 6 hours at 25°C. Vials are single use only. For oral solution: Once opened, discard after 7 months.
Storage	Store below 25°C.
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.[4]
Evidence summary	**Treatment of seizures in term infants:** Several case series have reported typical 70–80% response rates to levetiracetam when used either first line or for seizures refractory to other anti-epileptic drugs. Loading doses ranged from 10–50 mg/kg/day and maintenance dose 10 mg/kg/day titrated to a maximum of 80 mg/kg/day.[1, 5-9] (LOE IV) **Treatment of seizures in preterm infants:** Case series have reported typical 80% response rates to levetiracetam when used either first line or for seizures refractory to other anti-epileptic drugs. Loading doses ranged from 10–50 mg/kg/day and maintenance dose 10 mg/kg/day titrated to a maximum of 60 mg/kg/day.[9, 10] (LOE IV) **Safety:** There is currently insufficient evidence on the safety of levetiracetam in neonates.[3] However, levetiracetam use in neonates appears to be safe and efficacious in case reports so far although randomised controlled trials are lacking. **Pharmacokinetics:** Have not been reported in preterm infants.[1] The half-life in neonates is longer compared to older children.[1] 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.[1] The CL is lower in neonates and infants with renal impairment requiring monitoring of trough concentrations and dose adjustment.[1, 2] In children, the clearance was reported to be increased by 30% with co-administration of phenobarbital (phenobarbitone), carbamazepine and phenytoin.[11] In children aged 2–46 months, oral administration is characterised by rapid absorption, resulting in peak plasma concentrations within 1.4 hours of dosing and a half-life 5 hours.[12] Recommendations are to target levetiracetam trough concentration > 20 mg/L when seizure frequency is high and —10 - 40 mg/L subsequently titrated to seizure control.[1, 2, 16]
References	1. Loiacono G, Masci M, Zaccara G, Verrotti A. The treatment of neonatal seizures: focus on levetiracetam. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2016;29:69-74. 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;72:43-9. 3. Egunsola O, Choonara I, Sammons HM. Safety of Levetiracetam in Paediatrics: A Systematic

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