Ranibizumab (Lucentis) 2022

Newborn use only

Alert	For intravitreal injection by ophthalmologist only, after full informed parental consent.
Indication	Aggressive posterior ROP, Zone 1 Type 1 ROP, Posterior Zone 2 Type 1 ROP and as adjunct to failed laser treatment of ROP or where laser is not possible due to media opacity.
Action	Antineovascularisation agent. Binds to and inhibits vascular endothelial growth factor A (VEGF-A).
Drug type	Recombinant humanized IgG1 monoclonal antibody.
Trade name	Lucentis
Presentation	Lucentis vial intravitreal injection 2.3 mg/0.23 mL Lucentis pre-filled syringe intravitreal injection is available but not recommended as the barrel only marks the adult dose of 0.5 mg and any lesser dose cannot be identified.
Dose	**0.12 - 0.2 mg (refer to special comments).** **Dose can be repeated in 28 days if required.**
Dose adjustment	Not applicable.
Maximum dose	
Total cumulative dose	
Route	Intravitreal
Preparation	**<u>Lucentis vial 2.3 mg/0.23 mL (1)</u>** • Disinfect the rubber stopper of the vial with appropriate antiseptic swab. • Attach a 5 micrometre filter needle (18G) to a 1 mL syringe using an aseptic non-touch technique. • Push the blunt filter needle into the centre of the vial stopper until the needle touches the bottom edge of the vial. • Withdraw all liquid from the vial. • Ensure that the plunger rod is drawn back sufficiently when emptying the vial in order to completely empty the filter needle. • Disconnect the syringe from the blunt filter needle. • Aseptically and firmly attach an injection needle (33G needle preferred) onto the syringe. • Expel the air from the syringe and adjust the dose to the 0.02 mL mark on the syringe.
Administration	• Procedure should be performed by a suitably qualified ophthalmologist with experience with ROP and intravitreal injection in neonates using aseptic technique. • Obtain informed parental/carer consent. • Sedate the patient as required under the supervision of neonatologist. • If the infant is on CPAP, the presence of a CPAP mask is not compatible with an adequately isolated surgical field but Hudson prongs and the connecter “reversed” in direction should allow satisfactory draping and taping. As an alternative, high flow humidified nasal cannula (HHFNC) can be used if considered appropriate support. • Proceduralist to scrub and wear sterile gloves. • Dedicated nurse assistant to be present. All staff providing care for the infant are recommended to wear surgical masks. • Use topical povidone-iodine 5% as the skin and conjunctival sac preparation. Aqueous chlorhexidine 0.05% to 0.1% may be used in infants with hypersensitivity to povidone-iodine. Wipe off any excess solution from the lids/skin immediately to prevent skin irritation. The conjunctival sac should be thoroughly irrigated with normal saline immediately after the injection. • Use a small fenestrated sterile drape and stick the edges down with sterile steri-strips to isolate the surgical field. • Use frequent sterile topical amethocaine 0.5% to provide topical anaesthesia. A sterile cotton bud soaked with amethocaine 0.5% can be used to impregnate the injection site and give compression to lower intraocular pressure prior to injection. There is no requirement to give a subconjunctival injection of xylocaine as this creates chemosis and interferes with marking the injection site. • Stabilise globe with 0.12 Bonn ophthalmic microforcep. • Use Castroviejo ophthalmic caliper to measure and mark the location of the injection site, which is 1.5 mm posterior to the limbus, in the inferotemporal quadrant.

	• Compress globe for 20 seconds prior to injection with a sterile cotton bud. This lowers intraocular pressure by displacing aqueous and safeguards against the likelihood of CRA occlusion created by the pressure rise that accompanies intraocular injection. • Slowly inject ranibizumab into vitreous cavity using 30 or 33g needle. Needle entry point is 1.5 mm posterior to the limbus, in the inferotemporal quadrant and enter 3-4 mm into the vitreous cavity parallel to the visual axis so as to avoid the relatively larger and more spherical neonatal crystalline lens. • Perform indirect ophthalmoscope to ensure drug visible within vitreous cavity, lens is clear and central retinal artery (CRA) is perfusing. Apply gentle ocular massage if precarious and perform anterior chamber paracentesis (with 27g needle) if CRA obstructed due to increased intraocular pressure. • At the discretion of ophthalmologist, either preservative free lubricant or chloramphenicol eye drops may be applied at the end of the procedure and chloramphenicol eye drops may be continued three times a day for 3 days. • Ophthalmologist to review within 24 hours or sooner if excessive eyelid swelling to exclude endophthalmitis.
Monitoring	Watch for any eye swelling/bleeding Monitor vital signs (e.g. BP, heart rate, respiratory rate) throughout the procedure. Monitor for signs and symptoms of infection or ocular inflammation. Monitor thyroid function in view of povidone-iodine use during the procedure.
Contraindications	Hypersensitivity to the active substance or to any of the excipients. Active or suspected ocular or periocular infections. Active intraocular inflammation.
Precautions	Pre-existing arterial thromboembolic condition – a multidisciplinary team decision is required on a case by case basis to assess the possible impact of systemic absorption and systemic side effects.
Drug interactions	Not applicable.
Adverse reactions	Adverse effects reported in adults treated with anti-VEGF for macular degeneration: Ocular infection Ocular haemorrhages Endophthalmitis Retinal detachment, retinal tears Increased intraocular pressure Corneal injuries/inflammation Lens opacities/cataract Arterial thromboembolic events Neonatal data are lacking.
Compatibility	Not applicable.
Incompatibility	Not applicable.
Stability	Stable in the unopened tray at 25°C for 24 hours.
Storage	**Vial:** Store at 2°C to 8°C (refrigerate - do not freeze). Protect from light.
Excipients	Trehalose dihydrate, histidine hydrochloride monohydrate, histidine, polysorbate 20.
Special comments	New South Wales Paediatric Ophthalmology – ROP treating group consensus: Ranibizumab 0.2mg/0.02mL intravitreal injection is the preferred option given the negligible systemic suppression of VEGF compared to bevacizumab. This dose equates to 40% of the adult dose. 0.02mL is a workable dosage volume and is a simple draw up of 0.02mL from the supplied ampoule. Smaller volumes are technically difficult to reliably measure in a 1 cc syringe and amounts less than this volume are uncertain in the amount actually delivered in the eye. Lower dose of 0.12 mg has been reported to be efficacious in CARE-ROP trial, but for the reasons mentioned above, it is a small volume to work with.
Evidence	**Background** **Vascular endothelial growth factor (VEGF)** - A key regulator of angiogenesis in foetal life. In the normally developing retina, VEGF leads to the development of blood vessels from the optic nerve to the periphery. In preterm infants with disrupted angiogenesis, however, the expression and levels of VEGF differ markedly in the two different phases. While the levels are suppressed in the vaso-

obliterative phase, there is an overproduction/expression of VEGF, leading to abnormal vascular proliferation in the vaso-proliferative phase.(2)
Type 1 ROP: Retinal findings defined as type 1 ROP are: (1) Zone I ROP: any stage with plus disease; (2) Zone I ROP: stage 3 - no plus disease, (3) Zone II ROP: stage 2 or stage 3 with plus disease.(2)
Efficacy
Anti-VEGF for type 1 ROP: Sankar et al 2018, in Cochrane systematic review, evaluated the efficacy or safety of anti-VEGF agents compared with laser/cryotherapy in type 1 ROP.(2) Six randomised or quasi-randomised controlled trials involving 383 infants were included. Four trials compared intravitreal bevacizumab monotherapy with conventional laser therapy.(3-7) One trial compared ranibizumab monotherapy with laser therapy (8) and one study compared intravitreal pegaptanib plus conventional laser therapy with laser and cryotherapy.(9) When used as monotherapy, bevacizumab/ranibizumab did not reduce the risk of retinal detachment, pre-discharge mortality, corneal opacity requiring corneal transplant, or lens opacity requiring cataract removal. The risk of retreatment also did not differ between groups. Subgroup analysis showed a significant reduction in the risk of recurrence in infants with zone I ROP (RR 0.15, 95% CI 0.04 to 0.62), but an increased risk of recurrence in infants with zone II ROP (RR 2.53, 95% CI 1.01 to 6.32). There was a significant increase in the risk of recurrence of ROP in eyes that received bevacizumab (RR 5.36, 95% CI 1.22 to 23.50; RD 0.10, 95% CI 0.03 to 0.17). Infants who received intravitreal bevacizumab had a significantly lower risk of refractive errors at 30 months of age. No trial included in this meta-analysis reported neurodevelopmental outcomes.(2)

Li et al 2018, in their meta-analysis, compared the efficacy of anti-VEGF and laser treatments in type-1 and threshold ROP.(10) This study included 4 RCTs and 6 comparative non-randomised studies (CNS) involving 1158 patients. Retreatment incidence was significantly increased in anti-VEGF (OR 2.52; 95% CI 1.37 to 4.66; P = 0.003) compared to the laser treatment. Retreatment incidence was 6.8-21.4% and 1.4-14% in Anti-VEGF and laser groups respectively. Average time interval between initial treatment and retreatment was 7.5 weeks (95% CI 2.00, 17.08 weeks). The longest retreatment time was 17 weeks (postmenstrual age not more than 57 weeks). While the retreatment incidence was higher, anti-VEGF treatment was safer, with a relatively reduced incidence (OR 0.29; 95% CI 0.10 to 0.82; P = 0.02) of eye complications (corneal opacity, cataract, preretinal or intravitreal haemorrhage and retinal detachment). There was less myopia in comparison to laser therapy (WMD 3.03D; 95% CI 1.48 to 4.59; p=0.0001).(10)

A descriptive review by American Academy of Ophthalmology in 2018 analysed 5 RCTs and 7 comparative non-randomised case series found that intravitreal anti-VEGF therapy is as effective as laser photocoagulation for achieving regression of acute ROP. But, ROP recurrence rate was higher, indicating a vigilant and extended follow-up.(11)

Anti-VEGF preparations and doses for ROP: Of 14 studies (RCTs and comparative non-randomised studies), (4-9, 12-19), 12 studies (5 of them RCTs) evaluated bevacizumab, 2 studies evaluated ranibizumab and 1 study trialled pegaptanib. RCTs evaluating bevacizumab used 0.5 mg to 1.25 mg (Beat-ROP trial and Karkhaneh et al – 0.625 mg in 0.025 mL; Lepore et al – 0.5 mg in 0.02 mL; O'Keefe et al and Moran et al – 1.25 mg in 0.1 mL). Zhang et al in their RCT used 0.3 mg in 0.03 mL of ranibizumab.

Author	Study	Anti-VEGF	Dose
CARE-ROP trial (20)	RCT	Ranibizumab	0.12 mg versus 0.2 mg
Beat-ROP trial 2011 (6)	RCT	Bevacizumab	0.625 mg in 0.025 mL
Karkhaneh 2016 (4)	RCT	Bevacizumab	0.625 mg in 0.025 mL
Lepore 2014 (5)	RCT	Bevacizumab	0.5 mg in 0.02 mL
O'Keefe 2016 (7)	RCT	Bevacizumab	1.25 mg in 0.05 mL
Moran 2014 (16)	RCT	Bevacizumab	1.25 mg in 0.1 mL
Harder 2013 (13)	Case series	Bevacizumab	0.375 mg – 0.625 mg
Isaac 2015 (15)	Case series	Bevacizumab	0.625 mg in 0.025 mL
Hwang 2015 (14)	Case series	Bevacizumab	0.625 mg in 0.025 mL
Mueller 2016 (17)		Bevacizumab	0.625 mg in 0.025 mL

Lee 2010 (19)	Case series	Bevacizumab plus laser	0.5 mg in 0.02 mL
Walz 2016 (18)	Case series	Bevacizumab	Dose not reported
Zhang 2016 (8)	RCT	Ranibizumab	0.3 mg in 0.03 mL
Gunay 2017 (12)	Case series	Bevacizumab Ranibizumab	0.625 mg in 0.025 mL 0.25 mg in 0.025 mL

Summary on short term efficacy of anti-VEGF for primary treatment of type 1 ROP: Anti-VEGF is probably as efficacious as laser treatment for acute type 1 ROP but the necessity for retreatment is higher (up to 21.4%) in comparison to laser therapy (up to 14%). Incidence of eye complications and myopia were less in anti-VEGF group.

Ranibizumab dose comparisons: CARE-ROP study group performed a multi-centre, double blind randomised controlled trail to compare 2 doses of ranibizumab (0.12 mg vs 0.2 mg) in 19 infants (38 eyes) with ROP. Primary end point was the need for rescue therapy until 24 weeks after the initial treatment. Rescue therapy was defined as the need for either laser or anti-VEGF within 28 days of initial treatment or laser treatment at any time. Other outcomes were retreatment with the same anti-VEGF dose if ROP activity reappeared after 28 days of initial treatment. When analysed per eye, 94.4% of eyes in the 0.12 mg group and 92.9% in the 0.20 mg group reached 24 weeks post-treatment without need for rescue therapy. Two (5.2%) eyes required rescue therapy with full resolution. Recurrence of any ROP stage was more prevalent in the 0.20 mg group. Two infants in each group (8 eyes [21.1%]) had recurrences that were severe enough to warrant retreatment. Eleven eyes (55.0%) had full physiologic vascularization in the 0.12 mg group, and only 3 eyes (16.7%) achieved full vascularization in the 0.20 mg group suggesting that higher anti-VEGF doses may impede physiologic vascularization. Free plasma VEGF levels were measured before (baseline) and during the first six weeks after ranibizumab injection. Several VEGF levels were below detection limit at baseline (i.e. before ranibizumab injection). There was no sustained suppression of mean VEGF levels after ranibizumab injection in either group.(20)

Ranibizumab in zone II ROP: In a randomised controlled trial, Zhang et al compared 0.3 mg of ranibizumab and laser therapy for zone II ROP. A substantial proportion of infants developed recurrence of ROP after ranibizumab in comparison to laser therapy (52% versus 4%).(21)

Topical antibiotics during and following intravitreal injections: A descriptive review of adult studies did not find firm evidence supporting benefit for topical antibiotic prophylaxis for post-injection endophthalmitis and may carry harmful effects with possibly higher endophthalmitis rates and increasing antibiotic resistance. Firm evidence is lacking for neonates to recommend or refute the clinical practice.(22)

Topical antisepsis (povidone-iodine): A prospective randomised evaluation in adults of topical antibiotic plus povidone-iodine versus povidone-iodine alone showed that patients undergoing regular intravitreal injections, the rate of positive bacterial cultures was 8% in the group that received a three-day course of pre-injection topical gatifloxacin in addition to povidone–iodine immediately prior to injection, compared with just 4% in the group that received povidone–iodine alone (p = 0.32).(23)

Safety

Concerns remain regarding the potential long term local and systemic adverse effects of anti-VEGF.

Local eye complications: There was no significant difference in the incidence of corneal opacity with anti-VEGF.(6) Lens opacity was not found in 2 studies (4, 8) and one study did not find any difference in the incidence of cataract in anti-VEGF versus laser groups.(6) Endophthalmitis and vitreous haemorrhage were reported in 2 studies and did not find these complications.(4, 8)

Systemic absorption and serum VEGF levels: VEGF is an important neurodevelopmental growth factor in the early newborn period. Wu et al, in a prospective cohort study, measured serum VEGF levels for up to 12 weeks after intravitreal ranibizumab (0.25 mg) or bevacizumab (0.625 mg) in infants with ROP. Serum VEGF level significantly decreased between baseline and up to 8 weeks in bevacizumab group (P

	= 0.007). There was no significant difference in the serum VEGF level between baseline and up to 8 weeks in ranibizumab group (P = 0.212).(24) **Neurodevelopmental outcomes:** A study from the Canadian Neonatal Network demonstrated 3.1 times higher odds (95% CI 1.2 to 8.4) of severe neurodevelopmental disabilities in preterm infants born before 29 weeks' gestation and treated with bevacizumab, after adjusting for key confounders like gestation, gender, maternal education, Score for Neonatal Acute Physiology-II (SNAP-II) score, bronchopulmonary dysplasia, sepsis, and severe brain injury.(25) However, this comparison was adjusted for many infant variables but not ROP severity, and there was a significantly greater proportion of patients with zone I disease in the bevacizumab group. A retrospective study published by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network involved 405 preterm infants < 27 weeks gestation who were treated with either surgery or bevacizumab for ROP. Primary outcome was the composite of death or neurodevelopmental impairment. Composite primary outcome did not differ between the groups but the odds of death (aOR 2.54 [95% CI 1.42 to 4.55]; P = .002), a cognitive score <85 (aOR 1.78 [95% CI 1.09 to 2.91]; P = .02), and a Gross Motor Functional Classification Scale level ≥2 (aOR 1.73 [95% CI 1.04 to 2.88]; P = .04) were significantly higher with bevacizumab therapy.(26) Araz-Ersan et al evaluated 13 infants treated with combination intravitreal bevacizumab (0.625 mg) and laser therapy for ROP, compared with a birthweight and gestational age matched control group of children who had received laser treatment for ROP. They found no difference in the mean cognitive, language, or motor scores on the BSID III test. (27) Lien et al studied BSID scores at 24 months of age in 61 infants who had received either bevacizumab (0.625 mg) monotherapy, laser monotherapy, or a combination of bevacizumab and laser therapy (required for salvage therapy). The patients who required combination (salvage) therapy had a higher incidence of mental or psychomotor impairment, but there was no difference between the groups that had either modality as monotherapy.(28) **Pharmacokinetics** Pharmacokinetic data in adults with macular degeneration estimate that vitreous half-life of ranibizumab is about 9 days and on reaching the systemic circulation, ranibizumab has a short half-life of 2 hours. The systemic-to-vitreous exposure ratio for ranibizumab was estimated to be 1:90,000. The steady-state serum concentrations of total ranibizumab were at all times below the concentrations needed to reduce VEGF-A–induced endothelial cell proliferation in vitro by 50%.(29)
Practice points	
References	1. Lucentis. Novartis Pharmaceuticals Australia Pty Ltd. MIMS online. Accessed on 19 November 2020. 2. Sankar MJ, Sankar J, Chandra P. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. Cochrane Database of Systematic Reviews. 2018(1). 3. Geloneck M, Chuang A, Clark W, Hunt M, Norman A, Packwood E, et al. BEAT-ROP Cooperative Group. Refractive outcomes following bevacizumab monotherapy compared with conventional laser treatment: a randomized clinical trial. JAMA Ophthalmol. 2014;132(11):1327-33. 4. Karkhaneh R, Khodabande A, Riazi-Eafahani M, Roohipoor R, Ghassemi F, Imani M, et al. Efficacy of intravitreal bevacizumab for zone-II retinopathy of prematurity. Acta ophthalmologica. 2016;94(6):e417-e20. 5. Lepore D, Quinn GE, Molle F, Baldascino A, Orazi L, Sammartino M, et al. Intravitreal bevacizumab versus laser treatment in type 1 retinopathy of prematurity: report on fluorescein angiographic findings. Ophthalmology. 2014;121(11):2212-9. 6. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. New England Journal of Medicine. 2011;364(7):603-15. 7. O'Keeffe N, Murphy J, O'Keeffe M, Lanigan B. Bevacizumab compared with diode laser in stage 3 posterior retinopathy of prematurity: a 5 year follow-up. 2016. 8. Zhang G, Yang M, Zeng J, Vakros G, Su K, Chen M, et al. Shenzhen Screening for Retinopathy of Prematurity Cooperative Group. Comparison of intravitreal injection of ranibizumab versus laser therapy for zone II treatment-requiring retinopathy of prematurity. Retina. 2016;37(4):710-7.

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Authors Contribution

Original author/s	Srinivas Bolisetty, Jeremy Smith, Matthew Spargo, Kimberley Tan, Hughie Tsang
Evidence Review	Brian Darlow, Tim Schindler
Expert review	John Downie, James Smith, Caroline Catt, Nadkarni Shivram, Kate Leahy
Nursing Review	Eszter Jozsa, Kirsty Minter, Renae Gengaroli
Pharmacy Review	Jessica Mehegan, Wendy Huynh
Contributors	Nilkant Phad, Bhavesh Mehta, John Sinn, Carmen Burman, Jessica Mehegan, Michelle Jenkins, Wendy Huynh, Helen Huynh
Final editing and review	Thao Tran, Srinivas Bolisetty
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty