Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ranibizumab

Proprietary Product Name: Lucentis

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

September 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
AMD	Age related macular degeneration
AP-ROP	Aggressive posterior retinopathy of prematurity
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific Annex
AUC_{inf}	Area under the plasma concentration-time curve from time zero to infinity
CI	Confidence interval
C_{max}	Maximum plasma drug concentration
CMI	Consumer Medicines Information
CNFUN	Canadian Neonatal Follow-Up Network
CNN	Convolutional neural network
CNV	Choroidal neovascularisation
CRYO-ROP	Cryotherapy for Retinopathy of Prematurity (Study)
DLP	Data lock point
DME	Diabetic macular oedema
DNA	Deoxyribonucleic acid
EU	European Union
ICROP	International Conference on Ophthalmology and Retinal Problems
nAMD	Neovascular age-related macular degeneration
OR	Odds ratio
PD	Pharmacodynamic(s)
PDR	Proliferative diabetic retinopathy
PDT	Photodynamic therapy

Abbreviation	Meaning
PI	Product Information
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic/pharmacodynamic
PM	Pathologic myopia
PSUR	Periodic safety update report
RMP	Risk management plan
ROP	Retinopathy of prematurity
RVO	Retinal vein occlusion
SAS	Special Access Scheme
$T_{1/2}$	Half life
VEGF	Vascular endothelial growth factor
VEGF-A	Vascular endothelial growth factor A
VEGFR	Vascular endothelial growth factor receptor

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Outcome:	Withdrawn
Date of withdrawal:	14 January 2020
Date of entry onto ARTG:	Not applicable
ARTG number:	Not applicable
▼ *Black Triangle Scheme:*[1]	Not applicable
Active ingredient:	Ranibizumab (rbe)
Product name:	Lucentis
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road, Macquarie Park NSW 2113
Dose form:	Solution for injection
Strength:	2.3 mg/0.23 mL
Containers:	Vial
Pack size:	One
Approved therapeutic use:	Not applicable
Route of administration:	Intravitreal injection
Proposed dosage:	Single-use vial (adults and preterm infants) or single-use pre-filled syringe (adults only) for intravitreal use only. Use of more than one injection from a vial can lead to product contamination and subsequent ocular infection. Lucentis must be administered by a qualified ophthalmologist experienced in intravitreal injections. The recommended dose for Lucentis in preterm infants is 0.2 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.02 mL. Treatment of retinopathy of prematurity (ROP) is initiated with a single dose and can be given bilaterally on the same day.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Further treatment may be administered if there are signs of disease activity. The interval between two doses injected into the same eye should not be shorter than one month.

Product background

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register Lucentis (ranibizumab (rbe)) 2.3 mg/0.23 mL solution for injection for the following proposed extension of indications:

> *Lucentis is indicated in preterm infants for the treatment of retinopathy of prematurity (ROP).*

Retinopathy of prematurity (ROP) is a proliferative vascular disease of the developing retina affecting preterm neonates of low gestational age and low birth weight. In humans, retinal vascularisation begins at about 12 weeks and is completed by 36 to 40 weeks of gestation. Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis in fetal life. Infants born before term have an immature retina with a peripheral avascular zone. ROP develops if there is a disruption in the new vessel formation (angiogenesis) in this zone. In most cases the vascular changes of ROP regress with time, however, in some cases, they can lead to fibrous scar formation, visual distortion, retinal detachment, and blindness if left untreated.

The extent and severity of ROP is traditionally described in terms of location (zones; I to III);[2] severity (stages; 1 to 5), extent of retinal involvement (in clock hours; 1 to 12), and the presence of vascular dilatation and tortuosity (termed 'plus disease') according to the International Classification of ROP (ICROP) definitions (see Table 1).[3,4]

Table 1: International Classification of Retinopathy of Prematurity; stages and descriptions of the key observations in retinopathy of prematurity

Stages and descriptions of key observations in retinopathy of prematurity	
Stage 1	Demarcation line separating avascular from vascularised retina
Stage 2	Ridge arising in region of demarcation line
Stage 3	Extraretinal fibrovascular proliferation/neovascularisation extending into the vitreous
Stage 4	Partial retinal detachment
Stage 5	Total retinal detachment
Plus disease	Increased vascular dilatation and tortuosity of posterior retinal vessels in at least two quadrants of the retina

[2] Zone I: Innermost zone, a circle with a radius extending from the centre of the optic disc to twice the distance from the centre of the optic disc to the centre of the macula.
Zone II: The retinal area, extending outwards from the edge of zone I to the nasalora serrata (at the 3-o'clock position in the right eye and the 9-o'clock position in the left eye).
Zone III: The residual portion of retinal area anterior to zone II.
By convention, zones II and III are considered to be mutually exclusive.
[3] The Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Archives of Ophthalmology.* 1984, 102(8):1130-4.
[4] International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity Revisited. *Archives of Ophthalmology.* 2005, 123(7):991-9.

Stages and descriptions of key observations in retinopathy of prematurity	
Pre-plus disease	More vascular dilatation and tortuosity than normal but insufficient to make the diagnosis of plus disease
Type 1 ROP	Zone I: any stage ROP with plus disease as well as stage 3 ROP without plus disease Zone II; stage 2 or 3 ROP with plus disease
Type 2 ROP	Zone I: stage 1 or 2 ROP without plus disease Zone II: stage 3 ROP without plus disease

Source: Revised international classification of ROP (ICROP) 2005)[3,4]

The aim of treatment is to remove the stimulus for vessel growth by ablating the peripheral avascular retina. The current usual treatment is peripheral retinal laser photocoagulation, but laser treatment has potential complications including systemic (for example bradycardia, cyanosis) and local complications (for example, oedema, haemorrhage or burns).[5] Further, there are concerns regarding the risks of intubation and sedation on neurodevelopment;[6] adverse effects such as laser induced myopia;[7] visual field reduction;[8] and suboptimal visual results in cases of posterior ROP.[9]

As VEGF is a key factor in regulation of angiogenesis anti-VEGF agents have been explored study, as an alternative to laser. A multicentre randomised controlled trial, the BEAT-ROP trial, used an intravitreal injection of bevacizumab, an anti-VEGF agent, to treat type I ROP.[10] Compared with laser, bevacizumab reduced recurrence of ROP at 54 weeks postmenstrual age for zone I ROP but not for zone II. At 2.5 years of age, infants treated with bevacizumab also had decreased rates of severe myopia. Moreover, the injection is a short procedure and required only topical anaesthesia.

In Australia, there is no anti-VEGF agent on the Australian Register of Therapeutic Goods (ARTG) indicated for ROP at the time submission was under consideration. However, ROP treatment guidelines in some local health districts recommend the use of anti-VEGF agents in specific circumstances, including failure to respond to laser or when laser treatment is not possible.[11] However, there are concerns about systemic absorption of anti-VEGF agents (such as bevacizumab) and its effect on developing tissues (including brain), given its prolonged half-life and antiangiogenic effect.

[5] Tauro J. Women and Babies: Retinopathy of Prematurity. Sydney Local Health District Policy for Neonatal Medical and Nursing Staff, Royal Prince Alfred Hospital, 8 October 2018. https://www.slhd.nsw.gov.au/RPA/neonatal%5Ccontent/pdf/guidelines/RPAH_GL2018_006_ROP_final.pdf
[6] McCann ME, Schouten AN. (2014). Beyond Survival; influences of blood pressure, cerebral perfusion and anesthesia on neurodevelopment. *Paediatr Anaest*h, 24(1):68-73.
[7] Geloneck MM, Chuang AZ, Clark WL et al. (2014). BEAT-ROP Cooperative Group. Refractive outomces following bevacizumab monotherapy compared with conventional laser treatment: a randomized clinical trial. *JAMA Ophthalmol,* 132 (11):1327-1333.
[8] McLoone E, O'Keefe M, McLooe S et al. (2007). Effect of diode laser retinal ablative therapy for threshold retinopathy of prematurity on the visual field: results of goldmann perimetry at a mean age of 11 years. *J Pediatr Ophthalmol & Strabismus*, 44(3):170-173.
[9] Mutlu FM, Sarici SU. (2013). Treatment of retinopathy of prematurity: a review of conventional and promising new therapeutic options. *Int J Ophthalmol*, 382(9902):1445-1457
[10] Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. (2011). Efficacy of intravitreal bevacizumab for stage 3+Retinopathy of Prematurity. *N Engl J Med*, 364:603-15.
[11] Sydney Local Health District: Royal Prince Alfred Guideline 2018. Women and babies: retinopathy of prematurity. https://www.slhd.nsw.gov.au/RPA/neonatal%5Ccontent/pdf/guidelines/RPAH_GL2018_006_ROP_final.pdf

Ranibizumab is an anti-neovascularisation agent. It is a humanised monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A) produced in *Escherichia coli* cells by recombinant deoxyribonucleic acid (DNA) technology. Ranibizumab inhibits the binding of VEGF-A to its receptors vascular endothelial growth factor receptors 1 and 2 (VEGFR-1; and VEGFR-2) on the surface of endothelial cells, thereby reducing endothelial cell proliferation, vascular leakage and new blood vessel formation.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 10 November 2008 for treatment of neovascular (wet) age related macular degeneration (AMD) in adults. The current indications approved in Australia are:

> *Lucentis (ranibizumab) is indicated in adults for:*
>
> - *the treatment of neovascular (wet) age-related macular degeneration (AMD),*
> - *the treatment of visual impairment due to diabetic macular oedema (DME),*
> - *the treatment of proliferative diabetic retinopathy (PDR),*
> - *the treatment of visual impairment due to choroidal neovascularisation*
> - *the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM),*
> - *the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO).*

At the time the TGA considered this application, a similar application had been approved in the European Union (EU) (approved on 3 September 2019) for the following indication:

> *Lucentis is indicated in preterm infants for the treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease*

Similar applications for Lucentis for the treatment of ROP in preterm infants were under evaluation in Switzerland (submitted 4 December 2018) and Singapore (submitted 1 October 2019). There have been no referrals, withdrawals or rejections of similar applications in other countries.

On 5 October 2018, the TGA granted Lucentis a positive Orphan drug designation;[12] for the indication listed in the Product Background (see above).

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

[12] **'Orphan drugs'** are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs, the TGA waives application and evaluation fees for prescription medicine registration applications if a related **orphan designation** is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application, and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

Table 2: Timeline for Submission PM-2018-04902-1-5

Description	Date
Positive Designation (Orphan)	5 October 2018
Submission dossier accepted and first round evaluation commenced	2 January 2019
First round evaluation completed	31 May 2019
Sponsor provides responses on questions raised in first round evaluation	31 July 2019
Second round evaluation completed	16 September 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	5 November 2019
Sponsor's pre-Advisory Committee response	15 November 2019
Advisory Committee meeting	6 December 2019
Registration decision (Outcome)	Not applicable; withdrawn by sponsor on 14 January 2019
Completion of administrative activities and registration on the ARTG	Not applicable
Number of working days from submission dossier acceptance to registration decision*	Not applicable

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There is no biological, nonclinical and toxicology evaluation with this submission. However general advice from the nonclinical area of the TGA regarding the potential for ranibizumab to have systemic effects on the brain was as follows:

> 'There are no useful evaluated studies in neonatal or juvenile animals for ranibizumab examining distribution into the brain. The specific concern is the unknown effect of anti VEGF agents on the developing brain in a vulnerable population of neonates and the ability to cross the blood brain barrier. Prevention of entry of antibodies into the brain from blood will depend on the presence of tight junctions rather than other components of the blood-brain barrier (that is operation of various efflux proteins) that develop later. There is enough formation of the blood-brain barrier by Week 12 of gestation in humans to block albumin from entering the brain.[13] Ranibizumab is a little smaller (molecular weights of 48 kDa) than albumin (molecular weights of 66.5 kDa), but a similar result would be expected. However the tight junctions are discontinuous and in some regions of the brain, the brain-blood barrier is absent.[14]'

Clinical

In the clinical dossier, a single completed study, Study CRFB002H2301, also known as the RAINBOW trial;[15] provided pharmacokinetic (PK), pharmacodynamic (PD) and clinical data for the study period of 24 weeks. In addition, the first interim results of the RAINBOW Extension trial, Study CRFB002H2301E1;[16] provided clinical data for the study period up to 40 weeks.

Pharmacology

Pharmacokinetics

The pharmacokinetic/pharmacodynamic (PK/PD) evaluation set included 49 patients in the ranibizumab 0.2 mg group and 46 patients in the ranibizumab 0.1 mg group.

Sparse PK sampling occurred on Day 1 (within 24 hours after administration of intravitreal ranibizumab), Day 15 (window of 7 to 21 days after first administration of ranibizumab) and Day 29 (window of 22 to 28 days after first administration of ranibizumab) of the study.

Limited conclusions can be drawn from these descriptive data due to sparse data collection, wide sampling window and high inter-individual variability across dose groups and time. Overall, median ranibizumab concentrations were highest on Day 1 with 7 to 8 fold lower ranibizumab concentrations observed on Day 29.

[13] Virgintino D, Robertson D, Benagiano V et al. (2000). Immunogold cytochemistry of the blood-brain barrier glucose transporter GLUT1 and endogenous albumin in the developing human brain. *Brain Res Dev Brain Res,* 123(1):95-101.
[14] Laterra J et al. (1999). Blood—Brain Barrier. In: Siegel GJ, Agranoff BW, Albers RW, et al., editors. Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 6th edition. Philadelphia: Lippincott-Raven; Available from: https://www.ncbi.nlm.nih.gov/books/NBK28180/ viewed online 4th Nov 2019.
[15] Study CRFB002H2301, RAINBOW Study: RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity (RAINBOW). ClinicalTrials.gov Identifier: NCT02375971; EudraCT Number: 2014-003041-10.
[16] Study CRFB002H2301E1, RAINBOW Extension Study: An Extension Study to Evaluate the Long Term Efficacy and Safety of RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity. ClinicalTrials.gov Identifier: NCT02640664; EudraCT Number: 2014-004048-36.

The population PK/PD analysis was conducted to characterise the systemic exposure in pre-term infants and to assess the relationship between VEGF concentration and PK. The objectives of the modelling analysis were firstly to assess if the ranibizumab population PK model for adults;[17] describes the PK in the preterm infant ROP population and if needed to use preterm infant patient weight as a fixed covariate and adjust for creatinine clearance.

The elimination rate from the eye is stated to be 50% faster in preterm babies compared to adults (half-life ($T_{1/2}$) = 5.6 days versus 8.7 days) whilst the elimination rate from serum is 3 fold lower than in adults ($T_{1/2}$ = 0.3 days versus 0.09 days).

From the population PK/PD analysis, median systemic ranibizumab maximum plasma drug concentration (C_{max}) and area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) were 16 fold and 12 fold higher, respectively, in premature infants receiving intravitreal ranibizumab 0.2 mg per eye than in adults receiving ranibizumab 0.5 mg in one eye.

The population PK/PD model did not predict a relationship between systemic ranibizumab concentrations and systemic free VEGF concentrations. Also, there was no association demonstrated between systemic ranibizumab concentrations and free VEGF levels in the premature infants and no predicted sustained inhibition of free VEGF.

Pharmacodynamics

From the population PK/PD analysis, concentration versus effect was not able to be predicted as the effect is local. Although the median serum VEGF concentrations in the ranibizumab groups are lower than the laser group, the ranges of values are wide and thus no conclusions can be drawn. There was no data on vitreal VEGF.

Efficacy

Efficacy was examined in a single primary efficacy study, Study CRFB002H2301 (RAINBOW trial);[15] with outcome measures at 24 weeks after starting treatment. Additional data was provided from the first interim analysis of the ongoing extension study, Study CRFB002H2301E1-IA1 (RAINBOW Extension trial);[16] with outcome measures at 40 weeks after the initial treatment.

RAINBOW trial (Study CRFB002H2301)

The RAINBOW trial was a randomised, open label, controlled, multi-centre, pivotal clinical trial with three arms: intravitreal ranibizumab 0.1 mg (n = 77); 0.2 mg ranibizumab (n = 74); and laser ablation therapy (n = 74) for the treatment of ROP in preterm infants.

The primary objective of the study was to demonstrate that intravitreal ranibizumab 0.2 mg was superior to laser therapy in the treatment of ROP. Treatment success was measured by the absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after starting treatment. Post-baseline treatment was permitted if required. Eligible subjects had bilateral ROP with one of the following findings in each eye:

- zone I, stage 1+, 2+, 3 or 3+ disease;
- zone II, stage 3+ disease; and/or
- aggressive posterior retinopathy of prematurity (AP-ROP).

[17] Joshi A, Lu J, Jumbe N, et al. (2005). Population Pharmacokinetics of ranibizumab: structural model identification, mean population pharmacokinetic parameter estimation, and covariate analysis. Genentec, Inc Report 05-1181.

Results

A total of 218 preterm infants received baseline treatment. Baseline disease characteristics were generally comparable across the groups, apart from an imbalance in birth weight groups observed at Baseline. Mean gestational age was 26.1 weeks and mean chronological age at Baseline was 10.9 weeks.

Treatment success at Week 24 was as follows: 80.0% ranibizumab in the 0.2 mg group; 75.0% in the ranibizumab 0.1 mg group; and 66.2% in the laser group. The comparison of ranibizumab 0.2 mg versus laser odds ratio (OR) was 2.19 (95% CI: 0.9932, 4.8235), p = 0.0254.

As the primary endpoint did not reach statistical significance key secondary endpoints were not tested.

The proportion of patients with recurrence of ROP requiring any post-Baseline intervention at or before 24 weeks was higher in the ranibizumab groups (31.1% for ranibizumab 0.2 mg) than the laser group (18.9%).

Overall, the efficacy data provided favour the 0.2 mg dose rather than the 0.1 mg dose of ranibizumab. Numerically, treatment success was higher in the ranibizumab 0.2 mg group (80.0%) than ranibizumab 0.1 mg group (75.0%) and the presence of unfavourable structural outcomes at Week 24 was lower in the ranibizumab 0.2 mg group (1.4%) than ranibizumab 0.1 mg group (6.7%). Both were lower than the laser group (10.1%).

An individual component of the primary efficacy variable, the proportion of patients with unfavourable structural outcomes in either eye at or before 24 weeks, was lower for the ranibizumab 0.2 mg group (1.4%) and ranibizumab 0.1 mg group (6.7%) than the laser group (10.1%).

Conclusion

Preterm infants are a vulnerable study population and there are many practical difficulties in performing clinical studies in this population. The RAINBOW trial was a thoughtfully designed clinical study in the relevant patient population. The primary endpoint set a very high bar as infants were required to have no ROP or adverse structural outcomes.

Overall, the study did not demonstrate statistical significance for the primary endpoint. However, ranibizumab had numerically higher treatment success over laser (OR of 2.19). The RAINBOW trial was not powered to determine whether particular disease characteristics, such as location or severity of ROP, predict response to VEGF. Longer term visual acuity or developmental outcomes are not yet known.

RAINBOW Extension trial (Study CRFB002H2301E1)

Results of the first phase of the Study CRFB002H2301E1 (RAINBOW Extension trial);[16] evaluating long term efficacy and safety, provide data corresponding to 40 weeks after initial ranibizumab treatment in the Core Study CRFB002H2301;[15] were presented. During the extension study patients could receive treatment with ranibizumab, (either re-treatment if they were in the ranibizumab arms of RAINBOW trial or switch treatment for those who received laser).

The remainder of the study is observational up to the patient's fifth birthday.

The primary objective of the first interim analysis was to evaluate the absence of ocular structural abnormalities in both eyes at or before the Week 40 visit. There were 144 patients who had completed the Week 40 visit (n = 143) or discontinued (n = 1) at the time of the data cut-off for the interim analysis.

Results

The mean number of ranibizumab injections received up to the Week 40 visit for the RAINBOW Extension safety set was 2.3 and 2.6 in the ranibizumab 0.2 mg and ranibizumab 0.1 mg groups, respectively. There were 8 patients in the laser group who received ranibizumab injections.

Absence of ocular structural abnormalities were observed for 49 out of 50 (98.0%) patients in the ranibizumab 0.2 mg group, 50 out of 51 (98.0%) patients in the ranibizumab 0.1 mg group and 38 out of 43 (88.4%) patients in the laser group.

Recurrence (defined as persistence of disease requiring additional injections) of ROP up to Week 40 was higher in the ranibizumab group (26.0% in the ranibizumab 0.2 mg group and 35.3% in the ranibizumab 0.1 mg group) compared with the laser group (18.6%).

Safety

The RAINBOW trial provided 24 week safety data;[15] and the RAINBOW Extension trial provided data at 40 weeks from the initial injection.[16]

Overall the ocular adverse event (AE) profile of ranibizumab was generally consistent with the known ocular adverse event profile of ranibizumab in the adult population, and there were no major differences in non-ocular adverse events between the treatment groups.

Ocular AEs were reported for 30.1%, 40.8% and 33.3% patients in the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser groups, respectively. Retinal haemorrhage, conjunctival haemorrhage, conjunctivitis and ROP were the most common. A higher proportion of patients in the ranibizumab groups had AEs suspected to be related to study drug treatment or procedure than the laser group. The most common was conjunctival haemorrhage.

One patient in the ranibizumab 0.1 mg group had endophthalmitis suspected to be related to study treatment.

There were generally no major differences in the non-ocular AE profile between the treatment groups. The non-ocular events (respiratory events and infections) were mainly related to the comorbidity of the population and medical history. No clinically relevant difference compared to laser was observed.

Severe non-ocular AEs reported for 20.2% patients.

There were 12 deaths in the study, 4 subjects in each group. One death in the ranibizumab 0.1 mg group due to respiratory failure was suspected to be related to study medication.

The interim analysis of available safety data up to 40 weeks from the first treatment identified no new safety concerns.

Risk management plan

The most recently evaluated EU-risk management plan (RMP) was version 12.1 (14 August 2013, data lock point (DLP) not specified) and Australian specific Annex (ASA) version 2.0 (20 December 2013). A RMP update including EU-RMP version 17.2 (15 June 2018; DLP clinical trial data 30 June 2017; DLP post marketing data 5 October 2016) and ASA version 6.0 (17 August 2018) has also been reviewed by the TGA. In support of the extended indications, the sponsor has submitted EU-RMP version 18.0 (21 September 2018; DLP for clinical trial data 24 January 2018; DLP for post marketing data 31 May 2018) and ASA version 7.0 (12 November 2018).

The sponsor has submitted EU-RMP version 18.2 (17 June 2019; DLP for clinical trial data 24 January 2018; DLP for post marketing data 31 May 2018) and ASA version 9.0 (11 July 2019) at the second round of evaluation.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 3.[18]

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infectious endophthalmitis	✓†	–	✓	✓*
	Retinal detachment and retinal tear	✓	–	✓	✓*
	Intraocular inflammation	✓	–	✓	✓*
	Intraocular pressure increase	✓	–	✓	✓*
Important potential risks	Neurodevelopmental delay (ROP only)	✓	–	–	–
Missing information	Potential effect on diabetic retinopathy of stopping periodic anti-VEGF (diabetic macular edema (DME))	✓	–	–	–
	Long term effects on the progression of the condition CNV (other than neovascular (wet) age-related macular degeneration (nAMD))	✓	–	–	–
	Visudyne (verteporfin-photodynamic therapy (PDT)) given in combination with ranibizumab (PM)	✓	–	✓	–
	Long term safety of ranibizumab in the condition ROP	✓†	–	✓	–

*Patient educational materials only relate to currently approved indications (not ROP).
†Targeted questionnaires/checklists for the follow-up of endophthalmitis and for use in paediatric patients.

[18] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The following are the Delegate's considerations with regards to RMP evaluation:

- The proposed routine risk minimisation activities in the ASA are for the following risks:

  Infectious endophthalmitis, retinal detachment and retinal tear, intraocular inflammation, intraocular pressure increase and Visudyne (verteporfin-photodynamic therapy) or laser photocoagulation given in combination with ranibizumab (pathologic myopia). The sponsor has included 'long term safety of ranibizumab in the condition of ROP' as missing information in the ASA.
- Guardians and parents of premature infants will be provided with a patient leaflet that includes use of Lucentis in premature infants with ROP. The leaflet educates about the disease background, administration of the drug and how it works, contraindications, warnings, precautions and possible side effects, and advice to contact their treating physician if the baby develops eye pain or worsening eye redness.
- The additional risk minimisation activities include targeted questionnaires/checklists (for use in paediatric patients and including a record of gestational age at birth and birth weight) for all reported AEs from ROP patients treated with ranibizumab.
- The obligatory periodic safety update reports (PSUR) frequency is three years. The RMP area recommended PSURs be submitted no less frequently than annually for the first three years (if the new indication is approved).

Pharmacovigilance activities

The RMP area suggested Lucentis be included in the Black Triangle Scheme to capture AE in preterm infants. The RMP area considers the risk of neurodevelopmental delay an important potential risk, and the long term safety missing information. Additional pharmacovigilance activities regarding the long term safety risks include the ongoing RAINBOW Extension trial.[16]

The RAINBOW Extension trial follows patients enrolled in the initial RAINBOW trial till their fifth birthday. The patient's visual acuity will be assessed in the better seeing eye at the patient's fifth birthday. The sponsor proposes to report on neurodevelopmental outcomes. The last patient visit is expected to be in the final months of 2022 and a final report produced in 2023.

The RMP evaluator is satisfied with the RMP and has recommended that the ranibizumab (rbe) EU-RMP version 18.2, dated 17 June 2019 (data lock point for clinical trial data 24 January 2018; DLP for post marketing data 31 May 2018) with ASA (version 9.0, dated 11 July 2019), and any future updates be implemented as a condition of registration.

The RMP evaluator considered the ASA is now acceptable and notes that routine pharmacovigilance activity is considered acceptable in this instance as the proposed long term efficacy and safety study, RAINBOW Extension trial (Study CRFB002H2301E1), will proceed as part of the marketing authorisation in the EU.

Comment

The long term safety study, RAINBOW Extension trial, will evaluate patients up till their fifth birthday but will not report until 2023. Long term safety including neurodevelopmental delay will be assessed, but it is not clear at what time points and which measures will be used. The current risk mitigation strategies are not adequate to balance the severity of the potential risk.

Risk-benefit analysis

Delegate's considerations

ROP affects preterm neonates. Untreated it can result in detrimental visual outcomes including blindness. The current treatment is laser therapy but there are risks including those that result from sedation and intubation and adverse effects on visual fields.

A single completed study (the RAINBOW trial);[15] provides efficacy and safety data for treatment with ranibizumab in premature infants with ROP, with additional data from the first interim analysis of the ongoing extension study. The RAINBOW trial, which was a randomised, open label, controlled, multicentre trial with three arms (total n = 225), did not demonstrate statistical significance for the primary efficacy measure at 24 weeks. However, numerically, treatment success was higher in the ranibizumab 0.2 mg group than the laser group (OR 2.19).

The study was not powered to determine whether particular patient characteristics or disease characteristics, such as location or severity of ROP, predict response to VEGF. The study did not systematically report on levels of sedation or anaesthesia required across groups.

Safety data at 24 weeks (and the RAINBOW Extension trial study data at 40 weeks);[16] showed an ocular adverse event profile consistent with the known profile for intravitreal use in adults. Further, there were no major differences in non-ocular adverse events between ranibizumab and laser treatment groups.

Longer term data are required to determine the effects of potential systemic suppression of VEGF. Premature infants have very different systemic physiology compared to adults, children and infants due to differences in body fat and muscle, metabolism and renal function. Premature babies' eyes are not fully developed from a neurological and vascular perspective. There is a question of how much ranibizumab may enter through the blood brain barrier or how the intravitreal-systemic flow from a premature baby compares to an adult. The specific concerns are that anti-VEGF agents may affect neurodevelopment or other outcomes including vital organ development.

The findings of two North American retrospective cohort studies of preterm infants have reported statistically significant long term neurodevelopmental adverse outcomes in preterm infants treated with anti-VEGF agents compared to laser. However, there are many confounding factors that may have affected the results.

- Morin et al.,2016;[19] examined data extracted from the Canadian Neonatal Network (CNN) and the Canadian Neonatal Follow-up Network (CNFUN) database. Preterm infants treated with bevacizumab (n = 27) versus those treated with laser (n = 98) had higher odds ratio of severe neurodevelopmental disabilities at 18 months follow up, with lower motor development scores reaching statistical significance.
- Natarajan et al., 2019;[20] extracted data from Eunice Kennedy Shriver National Institute of Child Health and Human Development, Neonatal Research Network Centers database (National Institutes of Health, USA). A greater proportion of infants in the bevacizumab group died (14.4% versus 6.3%; adjusted odds ratio 2.54 (95% CI 1.42 to 4.55); p = 0.002) and the likelihood of having cognitive scores < 85 was 1.78 fold higher in the bevacizumab group (95% CI 1.09 to 2.91).

[19] Morin J, Luu TM, Superstein R, et al. (2016). Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. *Pediatrics*, 137(4):e20153218. doi:10.1542/peds.2015-3218
[20] Natarajan G, Shankaran S, Nolen TL, et al. (2019). Neurodevelopmental outcomes of preterm infants with retinopathy of prematurity by treatment. *Pediatrics,* 144(2):e20183537. doi:10.1542/peds.2018-3537

Proposed action

At this stage, it is uncertain whether the efficacy benefits for intravitreal ranibizumab outweigh the lack of long-term safety data and potential risk of neurodevelopmental delay. The Delegate is of the opinion that the application should be rejected until the long term outcomes of visual acuity, visual function and developmental outcomes are known.

Request for Advisory Committee on Medicines advice

1. Are the infants in the clinical study typical of those in which treatment would be indicated in clinical practice?

   Not all ROP requires treatment. The RAINBOW clinical trial inclusion criteria included retinal examination findings in each eye specifying the extent and severity of proliferative disease. Do the inclusion criteria applied in the RAINBOW trial match the clinical parameters currently used to determine if a preterm infant should be treated with laser ablation?

2. Please comment on the increased rate of recurrence of ROP with ranibizumab and the need for retreatment. Is this an important negative outcome?

   Laser is the established treatment and is efficacious but risks of ocular side effects and concerns about anaesthetic risk have resulted in the search for alternative treatments.

   In the RAINBOW trial initial bilateral treatment was followed by recurrence of ROP in approximately 31% in the ranibizumab treatment arm, requiring retreatment. The higher rates of retreatment in the ranibizumab groups expose patients to repeated risks of treatment/procedure related AEs, including sedation. In the pivotal RAINBOW trial the level of sedation required by patients receiving intravitreal ranibizumab was not systematically reported, but the sponsor noted that individual records show that some patients in the ranibizumab group required higher levels of sedation than others.

   What level of sedation is required for injection versus laser treatment? What level of pain/discomfort does the patient experience with injection versus laser treatment? Are there other differential risks in level of sedation required? Does the requirement for a general anaesthetic weight the clinical decision over choice of treatment?

3. How relevant are the differences in 24 week ocular outcomes reported in this study to long term functional visual outcomes?

   In the pivotal study, the primary efficacy variable was the absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after starting study treatment. How clinically important are these measures of disease severity and structural outcomes.

   Do they predict functional visual outcomes in a child's everyday life?

   Does this difference in structural ocular outcomes result in different ophthalmic follow up/intervention?

4. Are there benefits and risks not apparent from the efficacy and safety in the clinical study which should be considered when making a decision about this drug (for example, different amounts of pain or discomfort associated with treatment, different needs for sedation)?

   The odds of treatment success were two times higher for the ranibizumab 0.2 mg group than the laser group. But this was not statistically significant. Did the tight definition of treatment success, (both the absence of active ROP and absence of unfavourable structural outcomes in both eyes at 24 weeks) weight the study too heavily against ranibizumab?

In Australia, laser is the first line treatment but several local health district protocols include anti-VEGF agents in the treatment algorithm. In two North American retrospective non randomised cohort studies (bevacizumab versus laser) the reasons for the choice of laser surgery versus bevacizumab were not captured. The Canadian Neonatal Network cohort included 125 preterm infants of whom 22% (n = 27) were treated with bevacizumab and the rest with laser.[19] In the United States, the National Institute of Child Health and Human Development Neonatal Research Network Centerss cohort study 45% (n = 181) of subjects were treated with bevacizumab versus laser.[20] The choice of bevacizumab over laser may relate to the vulnerability of the preterm infant, for example in the United States study infants in the bevacizumab group had a lower median birth weight and longer conventional ventilator support. However, vulnerabilities and co-morbidities of individual preterm infants may be relevant in making real world treatment choices for ROP (injection versus laser).

Are there factors not apparent from the RAINBOW clinical trial that clinical experts take into account in treatment choice for ROP?

Are there benefits and risks not apparent from the efficacy and safety in the clinical study which should be considered when making a decision about this drug?

5. Please comment on the adverse development outcomes noted in the prospective observational studies. Do you consider the lack of long term safety data a significant enough concern to prevent registration?

   The key issue is the lack of long-term safety data, both ocular and systemic, with particular concern about systemic effects.

   There is no good data on the long term safety of both ocular and systemic outcomes of anti-VEGF agents. The RAINBOW Extension trial is planned to provide outcome data to subjects' fifth birthday. While the safety data up to Week 40 did not identify any new concerns, preterm infants are a vulnerable study population and assessing long-term safety outcomes in this patient population can be challenging.

   The degree of systemic absorption of anti-VEGF agents, and their systemic effects particularly on neurodevelopment are unknown, and an important potential risk. In the RAINBOW trial systemic exposures of premature infants to ranibizumab were 12 to 16 fold higher than in adults and 31% of infants required more than 1 injection of ranibizumab. The potential systemic suppression of VEGF cannot be excluded.

   In the adult population, safety data from patients receiving intravitreal anti-VEGF agents for retinal conditions have identified systemic safety risks including increased risk of stroke within subgroups of patients with higher baseline risks of stroke.[21]

   Two retrospective cohort studies (mentioned above) provide safety data on a different anti-VEGF agent, bevacizumab. Concerns arising from these studies are that poorer neurodevelopmental outcomes, deaths and the likelihood of having cognitive scores < 85 were higher in the bevacizumab group.

   Is it appropriate to approve this treatment before results of the long term safety study, which is currently underway, are analysed?

[21] Bressler NM, Boyer DS, Williams DF et al. (2012). Cerebrovascular accidents in patients treated for choroidal neovascularization with ranibizumab in randomized controlled trials. *Retina,* 32:1821-8

Advisory Committee considerations[22]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The proposed extension of indications considered by the ACM was:

> *Lucentis (ranibizumab) is indicated in preterm infants for the treatment of retinopathy of prematurity (ROP).*

The ACM agreed that Lucentis had an overall negative benefit-risk profile for the proposed extension of indications, as the evidence submitted did not satisfactorily establish the safety of the product. The ACM was of the view that the long term safety of the product is unclear; other similar products are used/available for this purpose; and that infants with ROP will not be disadvantaged if the current application is not approved.

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice.

1. Are the infants in the clinical study typical of those in which treatment would be indicated in clinical practice?

The ACM advised that the selection criteria for use of anti-VEGF treatment in the clinical studies was broader than that currently applied for 'off-label' use of anti-VEGF treatment in Australia. The ACM also advised that in regards to baseline ROP characteristics, the proportion of children with zone I and aggressive posterior ROP (AP-ROP) in the clinical study is much higher than what is typically seen in the Australian context. The ACM noted that approval of Lucentis for treatment of ROP using criteria from the clinical study would potentially result in many more children being treated with Lucentis than are currently being exposed to anti-VEGF agents in Australia at present.

2. Please comment on the increased rate of recurrence of ROP with ranibizumab and the need for retreatment. Is this an important negative outcome?

The ACM advised that the increased rate of recurrence of ROP with ranibizumab and the need for retreatment is an important negative outcome, and is also observable with bevacizumab. The ACM agreed that children who receive ranibizumab will require frequent close follow up for many months after initial treatment to ensure that the disease has not recurred, as anti-VEGF treatment will delay or halt normal retinal vascularisation.

3. How relevant are the differences in 24 week ocular outcomes reported in this study to long term functional visual outcomes?

The ACM was of the view that there was a low correlation between structural changes at 24 weeks and long term visual outcomes. The ACM noted that the multi-centre trial of Cryotherapy for Retinopathy of Prematurity Study (CRYO-ROP Study), which was published in 1988;[23] and followed up patients for 15 years, indicated that even at 15 years,

[22] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

[23] Cryotherapy for Retinopathy of Prematurity Cooperative Group, Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. *Arch Ophthalmol* 1988; 106(4)471-479.

there is the risk of retinal detachment in treated eyes. There are case reports of patients with recurrent ROP at 2 years after bevacizumab treatment.

4. ***Are there benefits and risks not apparent from the efficacy and safety in the clinical study which should be considered when making a decision about this drug (for example, different amounts of pain or discomfort associated with treatment, different needs for sedation)?***

The ACM noted that the benefits of intravitreal injections are that they are much quicker, less technically challenging and require less sedation (does not require a general anaesthetic) than laser treatment. The ACM advised that the training for a competent laser surgeon for ROP is difficult and may take a full fellowship year (or more in many cases).

However, the ACM expressed concern that despite the risks of intravitreal injections, including infection and traumatic injury to the eye, the ease of administration may lead to less skilled clinicians using this treatment, and that these clinicians may not be aware of the need for close observation over several months to monitor for possible recurrence of disease.

5. ***Please comment on the adverse development outcomes noted in the prospective observational studies. Do you consider the lack of long term safety data a significant enough concern to prevent registration?***

The ACM considered the lack of long term safety data to be of significant concern, particularly in regards to uncertainties regarding effects on mortality and neurodevelopment, but also related to effects on other body systems (for example, renal (including hypertension) and respiratory outcomes).

Given the safety concerns raised, particularly in relation to neurodevelopmental defects, the ACM was of the view that it would be preferable to have at least the two year safety outcomes of the RAINBOW trial before Lucentis were considered for registration, or ideally the five year outcomes. At a minimum, the ACM was of the view that safety data from a second pre-defined interim analysis of the ongoing RAINBOW Extension trial (Study CRFB002H2301E1, due for submission in second quarter of 2020) should be provided before registration were considered.

6. ***The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.***

The ACM considered whether rejection of the current application would disadvantage patients while long term safety data is collected for re-consideration. The ACM did not believe this would be the case as other products are used/available for this indication and, if not approved in the current application, Lucentis will still be available through the TGA's Special Access Scheme (SAS).[24]

General advice

The ACM noted that this product has been approved in the EU for the same indication. However, the ACM was of the view that the Australian clinical context is sufficiently different as to warrant a different decision on registration until such time as further safety data becomes available.

[24] The **Special Access Scheme** (SAS) allows certain health practitioners to access therapeutic goods (such as medicines, medical devices or biologicals) that are not included in the Australian Register of Therapeutic Goods (ARTG) for a single patient.

Outcome

The sponsor withdrew their submission on 14 January 2020 before a decision had been made by the TGA.[25]

[25] Sponsor clarification:
The sponsor acknowledged the ACM's view that the clinical efficacy was demonstrated but that the Australian clinical context warranted that safety data from the second pre-defined interim analysis of the ongoing Study H2301 were to be provided before registration was considered. However, acknowledging that the TGA's fixed milestone process did not allow for the review of the second pre-defined interim analysis Study H2301E1 as part of the application evaluation, the sponsor withdrew the submission with the intention to re-submit the application once the second interim analysis is made available.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au