Clinical Commissioning Policy
Ranibizumab in Retinopathy of Prematurity (2201) [230401P]

Publication date: 30 May 2023 version number: 1

Commissioning position

Summary

Ranibizumab is recommended to be available as a routine commissioning treatment option, where diode laser treatment is not suitable, for neonates with retinopathy of prematurity within the criteria set out in this document.

The policy is restricted to preterm neonates, and it is not recommended to be used in those age groups not included in the policy.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Executive summary

This policy is focused on preterm babies with retinopathy of prematurity and the use of ranibizumab in this population.

The independent evidence review returned evidence for ranibizumab, which is presented for a routine commissioning position.

Plain language summary

Retinopathy of prematurity (ROP) is a condition which can affect the eyes in preterm babies. As the condition is preventable, all preterm (<31 weeks' gestational age) or low birth weight (<1,501g birth weight) babies are screened for it. The condition affects blood vessels (which carry blood around the body) in a part of the eye called the retina. The retina is at the back of the eye. It detects light and sends messages to the brain, which allows us to see. In severe ROP, blood vessels do not develop the way they are meant to in the retina. These abnormal blood vessels grow because of a substance called vascular endothelial growth factor (VEGF) which is produced in unusually high levels in the eyes affected by ROP. These abnormal vessels can turn into damaging scar tissue which can lead to blindness in the most severe cases.

If severe ROP is diagnosed, treatment will be offered within 48 or 72 hours depending on the severity of the diagnosis.

Severe ROP is usually treated with laser therapy. This treatment works very well and reverses severe ROP about 90% of the time. Laser therapy produces small burns to areas of the retina without good blood supply, which in turn reduces the amount of VEGF produced in the eye, and this stops abnormal blood vessels from growing further. For most babies, one treatment is enough. However, 1 in 7 to 1 in 10 babies will need re-treatment, usually around 2-3 weeks later. Babies will require several regular eye check-ups in the first four weeks after treatment and annual follow up in the eye clinic to monitor their eyesight for vision problems up to age 5 years.

An alternative treatment includes using injections into the eye. In these cases, a drug called ranibizumab, an anti-VEGF solution, is injected inside the eyes using a precise injection system. This temporarily stops the action of VEGF, which reduces or reverses the growth of the abnormal vessels. This treatment has been shown to work well and can be easier to perform than laser. However, it requires many months of regular eye examinations afterwards. Up to 1 in 3 (31%) babies will need a second treatment within 4 months of the first treatment taking place. Follow up following ranibizumab in the first year is more frequent and intensive than with laser therapy, with regular follow up in the first six months followed by annual follow up to age 5 years.

What we have decided

NHS England has carefully reviewed the evidence to treat babies diagnosed with ROP with ranibizumab. We have concluded that there is enough evidence to make the treatment available at this time.

Links and updates to other policies

NHS England has no other policies relating to the use of ranibizumab in retinopathy of prematurity.

Committee discussion

See the committee papers for full details of the evidence.

The condition

ROP is a potentially blinding condition which occurs secondary to the interruption of the normal process of retinal blood vessel development following preterm birth. Babies at risk of ROP require regular ophthalmic screening to ensure the early detection and management of abnormal neovascular proliferation which may, if left untreated, result in tractional retinal detachment. However, even with meticulous screening and management, the risk of visual loss due to ROP cannot be completely eliminated.

ROP is a two-phase disease: the first phase is characterised by the detrimental effects of relative hyperoxia on the immature retina; in the second phase, vaso-proliferation is driven by retinal ischaemia (mediated by angiogenic factors such as VEGF). ROP screening is initiated at the start of the second phase of the disease process to enable the detection and timely treatment of potentially sight-threatening vaso-proliferative disease. All babies less than 31 weeks' gestational age (up to and including 30 weeks and 6 days) or less than 1,501g birth weight should be examined to screen for the presence of ROP.

The zone in which ROP develops is an important disease indicator. The more posterior the disease location, i.e., zone I or posterior zone II, the larger the area of unvascularised, ischaemic anterior retina and the more likely the risk of progression to severe disease warranting treatment. Stages 1–3 refer to the appearance of the ROP "lesion" at the junction of posterior vascularised and anterior avascular retina. Stages 4 and 5 refer to development of

partial and total retinal detachment respectively, due to traction from neovascularisation. ‘Plus disease’ refers to dilation and tortuosity of the retinal vessels observed within zone I only. ‘Pre-plus’ refers to vascular changes insufficient for the diagnosis of plus disease but that cannot be considered normal. The changes represent a spectrum of appearances from normal to plus disease (mild to severe). Aggressive retinopathy of prematurity (A-ROP) is a specific form of the disease, characterised by severe plus disease, flat neovascularisation, intraretinal vascular shunting, haemorrhages, and rapid disease progression.

ROP is classified using internationally agreed criteria of zone, stage, and the presence of ‘plus disease’ (1). A combination of zone, stage, and presence of ‘plus disease’ enables the screener to determine whether the disease warrants treatment.

Current treatments

The current standard treatment for ROP is diode laser treatment (retinal laser photocoagulation) to areas of avascular retina. The aim of this treatment is to permanently burn avascular retina, which leads to a reduction in the production of VEGF which drives the formation of abnormal blood vessels in advancing ROP. Retreatment with laser is needed in up 14% of eyes. Follow-up after laser treatment usually takes place 5-7 days after treatment and then weekly until there are signs of ROP regression, which can be performed in outpatients. Thereafter, there is yearly follow-up in a Paediatric Ophthalmology clinic up to 5 years.

Proposed treatments

Where current standard treatment with diode laser is not considered clinically suitable, ranibizumab is an alternative treatment option. Ranibizumab is a VEGF inhibitor administered via an intravitreal injection into the eye and can be delivered within minutes in a variety of settings including in Neonatal Intensive Care Unit (NICU) by the ophthalmologist using a topical anaesthetic/light sedation and sterile technique. Currently, ranibizumab is the only VEGF inhibitor licensed for ROP treatment and is licensed to treat ROP in the UK at a dose of 0.2 milligrams. The International Classification of ROP was updated in 2021 (1), and replaced the clinical definition of ‘aggressive posterior ROP’ (used in the license) with aggressive ROP (A-ROP). This updated clinical definition is used here, requiring off label use for aggressive ROP beyond the posterior retina. ROP retreatment is required in approximately 1 in 3 babies (31%) primarily treated with ranibizumab. Retreatment may be with either with ranibizumab or laser. Follow up after ranibizumab treatment takes place 1-2 days after treatment, then weekly for 4 weeks, fortnightly for a further 12 weeks, every 4-weeks for a further 8 weeks, and then an annual follow up to age 5.

Epidemiology and needs assessment

In terms of those eligible for screening for ROP 2014 estimates (2) report that over 8,112 babies in the UK (6,987 in England) were low birth weight (<1,500 grams) as estimated from England and Wales Office for National Statistics (ONS) data.

Based on the 2014 UK figures above, 327, 4% of the 8,112 low birthweight babies were treated for ROP (654 eyes treated) in the UK (2). Approximately 90% (295 babies, and 590 eyes) were treated with laser and 8% (26 babies and 52 eyes) with anti-VEGF drugs such as ranibizumab.

Current activity rates for treatment since 2014 are uncertain, with anti-VEGF treatment numbers likely to have varied in association with a range of factors:

- Population at risk: Increased survival: over the last 3 decades, there has been a trend observed in high income countries of increased survival of extremely premature infants as observed in the United States (3). These extremely premature infants would be the most likely to develop ROP. In England and Wales, there was an increase of extremely low gestational age (<24 weeks), those most at risk of ROP between 2014 and 2020. Specifically, in 2014 there were 712 babies <24 weeks in 694,610 live births in England

and Wales (1.03/1,000 live births) and this increased to 815 in 613,231 live births (1.33/1,000) in 2020.

- Screening uptake: National Neonatal Audit 2014 data (4) suggests that national on-time screening rates were 93%, while 97% were screened on-time, early or late. These rates increased in 2020 to 95.1% and 99.0% respectively suggesting that more babies with ROP might be identified for treatment in later years (5). Late and missed screening opportunities could impact on rates of treatable ROP; in 2020, 73 of the 321 babies (23%) of babies screened late or not at all were less than 30 weeks' gestation and had a birthweight of less than 1,000g (5). This meant they were at high risk of sight threatening disease.
- Clinical awareness of anti-VEGF agents: the proportions of ROP cases treated with anti-VEGF drugs compared to laser may have increased with increasing clinical awareness of anti-VEGF agents since the publication of large randomised controlled efficacy trials of anti-VEGF agents in 2011 and 2019 (6-8).

Evidence summary

An independent evidence review was conducted for the use of ranibizumab for babies diagnosed with retinopathy of prematurity. NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of this treatment for the indication. The evidence review which informs this commissioning position can be accessed here: www.england.nhs.uk/publication/ranibizumab-in-retinopathy-of-prematurity/

Implementation Criteria

Inclusion criteria

To be eligible for treatment with ranibizumab, babies should be diagnosed with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) in line with the licence.

Patients with A-ROP (aggressive ROP beyond the posterior retina) disease are also eligible for treatment with ranibizumab. This use is off label.

Exclusion criteria

Babies who meet the following exclusion criteria will not be considered for treatment under this policy:

- Signs of ocular or periocular infection, **OR**
- Allergy to any component of the drug.

Starting criteria

Where current standard treatment with diode laser is not considered clinically suitable, and babies that meet all the inclusion criteria and do not meet the exclusion criteria should be considered for treatment with ranibizumab injections. Babies should be clinically evaluated to assess whether laser or ranibizumab is the more appropriate treatment on a clinical basis. Clinicians should ensure parents/carers are involved in every stage of the baby's treatment and that shared decision making is used to enable parents/carers to make informed decisions.

For vulnerable patients groups for whom follow up appointments may be challenging to access by carers, a documented discussion between available multi-disciplinary team members should take place to support this decision. The injection can be performed in a Neonatal Intensive Care Unit by an ophthalmologist using a topical anaesthetic/light sedation and sterile technique within a few minutes. This requires standard neonatal nurse monitoring to support the baby during the procedure.

Patients should receive the initial dose of 0.2 milligrams and use of a low volume high accuracy syringe (0.02ml) should be considered. Treatment of ROP is initiated with a single injection per

eye and may be given bilaterally on the same day. In total, up to three injections per eye may be administered within six months of treatment initiation if there are signs of disease activity. Most patients (78%) in the clinical study received one injection per eye. The administration of more than three injections per eye has not been studied. The interval between two doses injected into the same eye should be at least four weeks. Treatment should be initiated within 48 hours for those diagnosed with A-ROP or zone I stage 3 with Plus disease. Treatment should be initiated within 48-72 hours for all other forms of disease.

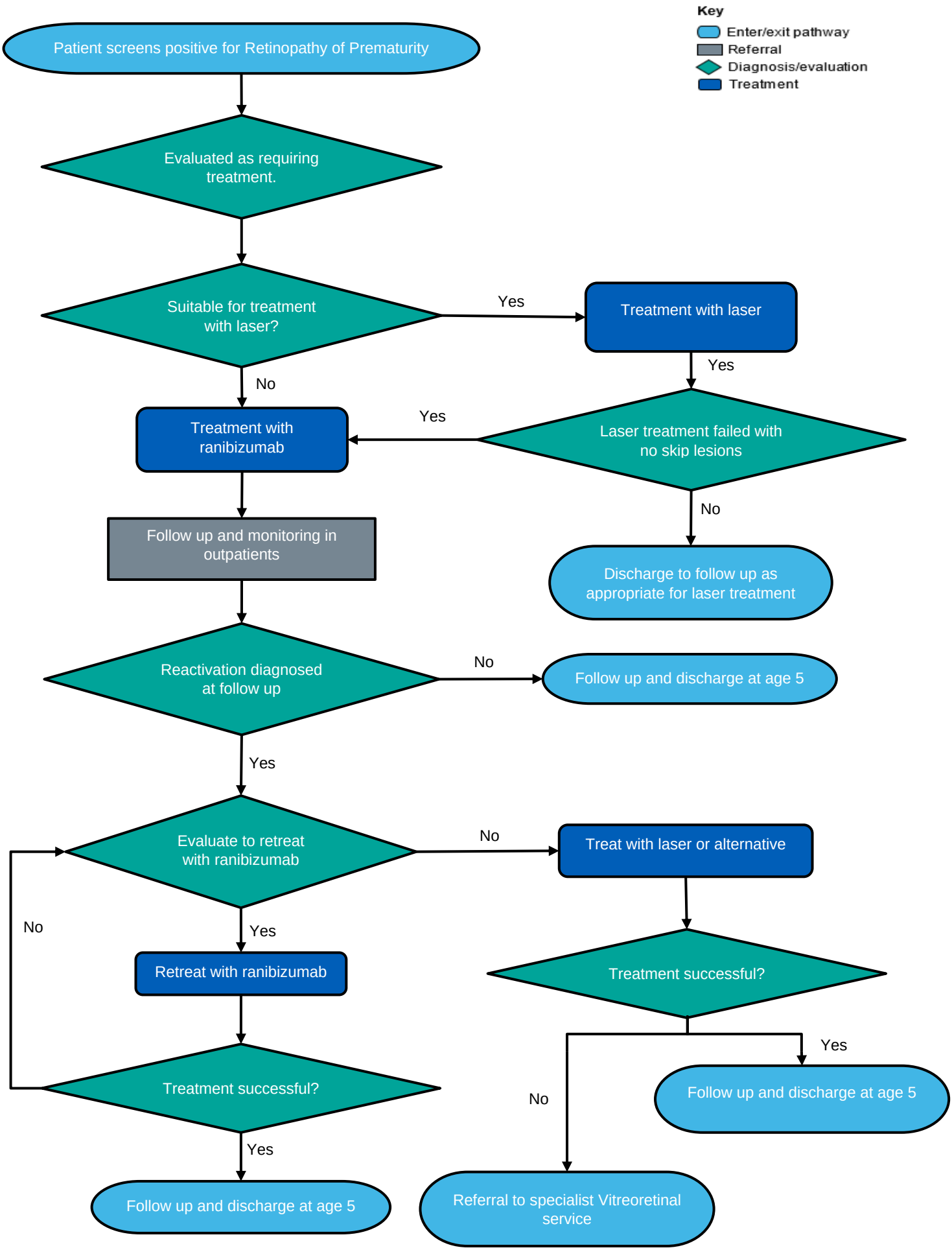
Reassessment

Patients should be followed up after a ranibizumab injection after 1-2 days, then weekly for 4 weeks, fortnightly for a further 12 weeks and then every 4-weeks for a further 8 weeks, to look closely for signs of late reactivation; this can all be performed in outpatients but occasionally examination under anaesthesia may be required. Thereafter, there is yearly follow-up in Paediatric Ophthalmology clinic up to 5 years.

Stopping criteria

Treatment should be stopped when a total of three doses have been given to an eye (two retreatments), or 24 weeks after the initial treatment, whichever is the earlier.

Patient pathway



Governance arrangements

This policy should be used in conjunction with the Specialised Ophthalmology (Paediatrics) https://www.england.nhs.uk/wp-content/uploads/2013/06/d12-spec-ophthalmo-paed.pdf Service Specification and Neonatal Critical Care https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/e08-serv-spec-neonatal-critical.pdf service specification.

The use of ranibizumab is off label when used for treatment of aggressive ROP beyond the posterior retina. Any provider organisation treating babies with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

The proposed mechanism for funding is via established mechanisms for high-cost tariff-exempt drugs to NHS England specialised commissioning teams.

Audit requirements

All patients receiving ranibizumab for ROP should be registered with the European EU-ROP registry (www.eu-rop.org). Local collection of data is mandated and should be audited annually. This information is collected to inform future revisions of this policy.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Retinopathy of prematurity	Retinopathy of prematurity (ROP) is an eye disorder caused by abnormal blood vessel growth in the light sensitive part of the eyes (retina) of premature babies.
Ranibizumab	A treatment inhibiting vascular endothelial growth factor (VEGF)
Vascular endothelial growth factor (VEGF)	A substance made by cells that stimulates new blood vessel formation
Aggressive Retinopathy of Prematurity (A-ROP)	An uncommon, rapidly progressive, severe form of ROP characterised by the prominence of plus disease and the ill-defined nature of the retinopathy

Plus Disease	Plus disease refers to dilation and tortuosity of the retinal vessels within zone I (only)
ROP Stage	Six stages (1, 2, 3, 4a, 4b and 5) which describe the severity of ROP from stage 1 (very mild disease) to stage 5 (complete retinal detachment). Stages are defined in the ICROP 3rd edition classification[1]
ROP Zone	Three zones (I, II, and III) centred on the optic disc The zone in which ROP develops is an important disease indicator. The more posterior the disease location, i.e., zone I or posterior zone II, the larger the area of unvascularised, ischaemic anterior retina and the more likely the risk of progression to severe disease warranting treatment

References

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2. Adams GG, Bunce C, Xing W, Butler L, Long V, Reddy A, et al. Treatment trends for retinopathy of prematurity in the UK: active surveillance study of infants at risk. BMJ Open. 2017;7(3):e013366.
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7. Marlow N, Stahl A, Lepore D, Fielder A, Reynolds JD, Zhu Q, et al. 2-year outcomes of ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW extension study): prospective follow-up of an open label, randomised controlled trial. Lancet Child Adolesc Health. 2021;5(10):698-707.
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