NHS
Wiltshire
Clinical Commissioning Group

## General Commissioning Policy

| Treatment | Intra-vitreal Therapies |
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| For the treatment of | Eye disease. |
| Background | This commissioning policy is needed in order to clarify the eligibility criteria for the use of intra-vitreal therapies (including injections of Lucentis [Ranibizumab] and Eylea [Aflibercept]) in patients with visual impairment caused by a variety of eye diseases, including Wet Age Related Macular Degeneration (ARMD). The therapies and indications covered are:<br>➢ **Lucentis / Eylea for Wet AMD**<br>➢ **Lucentis / Eylea / Iluvien/ Ozurdex for Diabetic Macular Oedema (DMO)**<br>➢ **Lucentis / Ozurdex / Eylea for Retinal Vein Occlusion (RVO)**<br>➢ **Lucentis for Myopic Choroidal Neovascularisation (CNV) / Inflammatory CNV**<br>➢ **Jetrea for symptomatic vitreo-macular traction/macular hole** |
| Commissioning position | NHS Wiltshire CCG commissions the use of intravitreal therapies in eye disease as set out below:<br>**A) Wet Age Related Macular Degeneration (ARMD)**<br>Ranibizumab therapy is routinely commissioned in line with NICE TA155[1], where **all** of the following circumstances apply in the eye to be treated:<br>• The best possible visual acuity (VA) after correction with glasses or contact lenses is between 6/12 and 6/96.<br>• There is no permanent damage to the fovea<br>• The area affected by ARMD is no larger than 12 times the size of the area inside the eye where the optic nerve connects to the retina.<br>• There are signs that the condition has been getting worse. (ie. blood vessel growth, as indicated by fluorescein angiography, or recent VA changes)<br>**and**<br>• The manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012).<br>NB. Treatment should be stopped if [2]:<br>• Vision in the treated eye falls below 15 letters (absolute) on 2 consecutive visits in the treated eye, attributable to AMD<br>• Vision falls by 30 letters or more compared to the best recorded vision since baseline<br>• There is evidence of deterioration of the lesion morphology despite treatment.<br>Requests for treatment in patients with wet ARMD where the above NICE criteria are not met must be submitted for consideration to the NHS Wiltshire CCG IFR (Individual Funding Request) Panel outlining the rationale for expected clinical benefit. Such cases might include those where visual loss is due to fluid rather than scarring or where vision in the other eye is already poor.<br>Aflibercept (Eylea) is an alternative, licensed (Nov 2012) intra-vitreal injection for wet ARMD, recommended in the NICE TAG 294[3] which uses the same eligibility criteria as NICE TA155[1]. Both aflibercept and ranibizumab have the same mode of action and are equivalent in terms of efficacy and safety[4]. |

NHS Wiltshire CCG commissions the use of aflibercept in patients with wet age-related macular degeneration if:

- it is used in accordance with the eligibility criteria for ranibizumab in NICE TA155[1]

**and**

- the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.

Requests for treatment with aflibercept in patients with wet ARMD where the above criteria are not met must be submitted for consideration to the NHS Wiltshire CCG IFR (Individual Funding Request) Panel.

**B) Diabetic macular oedema (DMO) / retinopathy:**

Ranibizumab therapy is routinely commissioned in line with NICE TA274[5] in patients where:

- the eye has a central retinal thickness of 400 micrometres or more at the start of treatment

**and**

- the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012).

Aflibercept injection is also recommended as an option for treating visual impairment caused by diabetic macular oedema[6] as per the criteria above for ranibizumab.

In addition, in line with NICE TA301[7] Wiltshire CCG routinely commissions Fluocinolone acetonide (Iluvien) intravitreal implants for people with chronic DMO who have an intra-ocular lens implant in the eye to be treated if:

- their diabetic macular oedema has failed to respond to other treatments.

Dexamethasone intravitreal implant (Ozurdex) is routinely commissioned as per NICE TA349 (July 2015)[8] where it is recommended as a possible treatment for people with sight problems caused by diabetic macular oedema if:

•there is an artificial lens in the eye to be treated, and

•their diabetic macular oedema has not improved with non-corticosteroid treatment, or such treatment is not suitable for them.

Requests for treatment in patients with DMO where the NICE criteria are not met must be submitted for consideration to the NHS Wiltshire CCG IFR Panel.

**C) Macular oedema due to retinal vein occlusion (RVO)**

Ranibizumab therapy is routinely commissioned as an option for treating visual impairment caused by macular oedema in line with the criteria in NICE TA283[9]:

- following central retinal vein occlusion (CRVO);

**or**

- following branch retinal vein occlusion (BRVO) as per the NICE TA for aflibercept in BRVO (September 2016)[11], so laser treatment (grid laser photocoagulation) does NOT have to be tried first-line.

**and**

- only if the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012).

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| | NHS Wiltshire CCG also routinely commissions the use of Ozurdex in line with NICE TA229[10] for patients where laser therapy has failed or is contraindicated due to extensive haemorrhage.<br><br>NHS Wiltshire CCG also routinely commissions the use of Eylea (Aflibercept) in line with NICE TA305[12] as an option for patients with central retinal vein occlusion (CRVO) only if the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.<br>NICE have recently published the Technology Appraisal[11] for the use of aflibercept for BRVO which states:<br>• Aflibercept is recommended as an option within its marketing authorisation for treating visual impairment in adults caused by macular oedema after branch retinal vein occlusion, only if the company provides aflibercept with the discount agreed in the patient access scheme.<br>NHS Wiltshire CCG commissions the use of aflibercept as per the NICE recommendation above.<br>Requests for treatment in patients with RVO where the NICE criteria are not met must be submitted for consideration to the NHS Wiltshire CCG IFR Panel.<br><br>**D) Myopic Choroidal Neovascularisation (Myopic CNV)**<br>NHS Wiltshire CCG routinely commissions Ranibizumab therapy as an option for treating visual impairment caused by myopic CNV in line with the criteria in NICE TA298[13] only if the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012).<br><br>**E) Inflammatory CNV**<br>Ranibizumab has now been licensed for this indication. Our policy for use in this indication can be found here:<br>http://www.wiltshireccg.nhs.uk/wp-content/uploads/2013/12/Ranibizumab-Funding-Policy-2017.03.01.pdf<br><br>**F) Visual Loss due to Vitreo-Macular Traction**<br>NHS Wiltshire CCG routinely commissions Ocriplasmin (Jetrea, single injection) therapy as an option for treating visual impairment in adults caused by vitreomacular traction in line with the criteria in NICE TA297[14], where the following criteria are met:<br>• no epiretinal membrane (a thin layer of scar tissue over their retina, the light-sensitive area at the back of the eye)<br>and<br>• a macular hole (up to 400 micrometers) in the centre of their retina<br>or<br>• severe sight problems.<br><br>**G) Other eye disease**<br>Requests for treating other rarer eye diseases with intra-vitreal therapies outside licensed indications must be submitted to the NHS Wiltshire CCG IFR Panel for consideration together with accompanying evidence of previous treatments and the expected clinical benefit from the requested treatment. |
| **Effective from** | 1st October 2016 |
| **Summary of evidence /** | **A)** Wet Age Related Macular Degeneration<br>NICE TA155[1] considered data from 4 RCTS: MARINA, ANCHOR, PIER |

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| **rationale** | and FOCUS trials. The 3 published trials[15-17] reported mean increases in visual acuity in the 0.5 mg ranibizumab group compared with baseline.<br>In addition, for wet ARMD aflibercept showed equivalence to ranibizumab (given monthly) when studied within the VIEW 1+2 RCTs[4]. It can be given as an automatic 2 monthly dose in the first year (7 injections in total) - compared to a mean of 6 injections with ranibizumab as required - but the fixed aflibercept dosing reduces the need to assess the eye regularly and allows partial booking of the first year of treatment. In the second year of the VIEW studies; aflibercept and ranibizumab were again compared head to head using an as required 'prn' regime and again both drugs showed equivalence. The mechanism of injection and the safety profile appear identical between the two drugs.<br><br>**B)** Diabetic macular oedema (DMO) / retinopathy<br>NICE TA274[5] concluded treatment of DMO with ranibizumab was cost effective as long as patients could access a discounted drug cost via the patient access scheme and there was a more tightly defined eligibility criteria, ie. patients with greater than 400 micrometres of diabetic macular oedema. Evidence came from the RESTORE trial[18] which showed gains in best corrected VA with ranibizumab were greatest in the subgroup of people with central foveal thickness greater than 300 micrometres, with no evidence for a benefit in adding laser to ranibizumab.<br>The Fluocinolone acetonide intravitreal implant (Iluvien) contains a corticosteroid that has anti-inflammatory and anti-vascular endothelial growth factor properties. It is administered by intravitreal injection and each implant releases 0.2 micrograms of Fluocinolone acetonide per day for approximately 3 years. Eligibility criteria for the use of the Iluvien in DMO is more restrictive than for ranibizumab, and despite it being substantially more expensive it has the advantage that 70% of patients will only need 1 injection over 3 years.<br><br>**Ci)** Macular oedema due to central retinal vein occlusion (CRVO)<br>CRVO has been untreatable until recently and patients with this condition have a very poor natural history. Of those presenting with vision poorer than 6/60, only 20% get any spontaneous visual improvement. Prior to the advent of intra-vitreal therapies the central visual loss in these patients would have been untreatable. The CRUISE trial[18], a phase III prospective, randomized, double masked, multicentre clinical trial involving 392 patients with CRVO, indicated that a 6 month improvement in VA is maintained after ranibizumab therapy. The mean letter gain is 14.9 letters with monthly 0.5mg ranibizumab injections versus 0.8 letters with sham treatment. ($p<0.0001$). The safety profile was consistent with previous phase III ranibizumab trials for wet ARMD with no new safety events for CRVO. |
| | **Cii)** Macular oedema due to branch retinal vein occlusion (BRVO)<br><br>Some patients with BRVO get better spontaneously in the first year, so the RCOphth recommends initially observing for 3 months prior to considering macular argon laser therapy if the patient's vision is between 6/12 and 6/60 and the condition has been present for 3 to 12 months. However argon laser can generate ocular co-morbidity including central scotoma, visual loss and late onset choroidal neovascularisation.<br>In patients for whom treatment with laser photocoagulation either has |

not been beneficial or is deemed unsuitable due to the extent of macular haemorrhage or ischaemia, ranibizumab is commissioned as a treatment option.

The BRAVO trial[20] a phase III prospective, randomized, double masked, multi-center clinical trial involving 397 patients with BRVO showed better reversal of visual loss at 6 months with monthly 0.5mg ranibizumab injections than sham treatment. BRVO patients gained a mean number of 7.3 letters with sham compared to a mean of 18.3 letters with ranibizumab 0.5mg at month 6 ($p<0.0001$).

Rescue laser was allowed after 3 months of follow-up and was performed in 54.5% of the sham group compared to only 19.8% in the ranibizumab group. The safety profile was consistent with previous phase III ranibizumab trials for wet ARMD with no new safety events for BRVO.

NICE noted that in both BRAVO and CRUISE ranibizumab was associated with statistically significant mean gains in BCVA in the treated eye compared with sham injection for the 6-month treatment phase. It also noted that ranibizumab was associated with sustained gains in BCVA at 12 months in both BRAVO and CRUISE, and that these were statistically significant ($p<0.01$ and $p<0.001$ respectively).

Ozurdex (dexamethasone implant) is also recommended by NICE as an option for treating retinal vein occlusions. Evidence came from the 2 GENEVA trials[21] multi-center, randomised, parallel group, sham-controlled studies with identical designs, involving 1,267 patients with macular oedema secondary to BRVO or CRVO. Both studies consisted of an initial 6-month masked phase, followed by a further 6- month, open-label period. In the initial 6-month phase patients were randomised to receive a single administration of either DEX 700µg intravitreal implant or sham (needleless applicator). In the open-label phase, patients received a single administration of DEX 700µg intravitreal implant.

The primary outcome measure was the time to achieve a ≥ 15 letter improvement in BCVA and pooled analyses showed this was significantly less with DEX 700µg intravitreal implant versus sham ($P < 0.001$), with differential improvements in VA apparent as early as day 30. The proportion of patients achieving a ≥ 15 letter improvement in BCVA was significantly higher from day 30 to day 90 ($P <0.001$).

It should be noted that there is an increased risk (6x) of cataract development in eyes treated with Ozurdex. In addition glaucoma can be precipitated by Ozurdex and around 25% of patients in the GENEVA study required topical glaucoma treatment whilst 0.9% needed a procedure as a consequence of Ozurdex treatment.

Evidence for Eylea (Aflibercept) in patients with Central Retinal Vein Occlusion (CRVO) comes from two phase III prospective, randomized, double masked, multicentre clinical trials; GALILEO AND COPERNICUS. In these patients were treated monthly for 6 months and then prn out to 2 years.

Patients gained on average +17.3/+18 letters at 24 weeks vs -4.0/+3.3 letters in the sham treatment arms. In addition 60% of patients gained 15 letters of vision with Eylea vs 22-32% of sham treated patients.

Patients needed on average 8.5 injections in the first year compared to 9.3 injections at 1 year in the CRUISE study[21] (Lucentis for CRVO)

**D)** Myopic CNV

Patients with CNV caused by pathological myopia previously offered photodynamic therapy (PDT) did well at avoiding 8 letters of visual loss at 1 yr with PDT. However long term benefit is often lost due to retinal pigment epithelial atrophy[22]. Recent evidence suggests ranibizumab

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| | therapy in these patients can deliver an average mean 12.78 letter gain in an eye with no prior treatment at 12 months and that eyes previously treated with PDT may not achieve such a good prognosis[23]. Most patients with myopic CNV are young and given the guarded prognosis with PDT are keen to regain vision and would opt for Lucentis therapy, which is now recommended as a treatment option by NICE[12].<br>PDT should however remain available according to patient preference eg for those who are needle phobic.<br><br>**E)** Inflammatory CNV<br>See policy: http://www.wiltshireccg.nhs.uk/wp-content/uploads/2013/12/Ranibizumab-Funding-Policy-2017.03.01.pdf<br><br>**(F)** Visual Loss from Vitreo-Macular Traction<br>Vitreo-retinal traction is a degenerative condition in which the vitreous gel in the centre of the eye is pathologically adherent to the retinal surface causing structural damage that can impair the vision. Previously the only option was surgery to remove the vitreous gel but the use of one Ocriplasmin injection in the affected eye gives an alternative less invasive treatment option for some patients[24]. Repeat injections are not recommended. |
| **Lifestyle factors** | Smoking[25]: Tobacco smoking is the main modifiable risk factor for AMD. Current smokers have a 2-3 fold increased risk of developing AMD and there is a dose-response relationship with pack-years of smoking. Therefore patients must be referred to stopped smoking services, and have the risks of continued smoking explained to them. |
| **Date** | 1st October 2016 |
| **Review date** | September 2017 |
| **Contact for this policy** | NHS Wiltshire Clinical Commissioning Group. |

This Policy will be reviewed in the light of new evidence, or guidance from NICE.

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