Adult (age≥18 years) treatment pathway with anti–vascular endothelial growth factor therapy for wet age-related macular degeneration based on NICE TAs 155, 294, 672 & 800 and local agreements

Does the patient have **Wet age-related macular degeneration (w-AMD)?**

Does the patient meet NICE initiation criteria for of Anti–vascular endothelial growth factor (anti-VEGF) therapy?
Do all the following circumstances apply in the eye to be treated?

- the best-corrected visual acuity is between 6/12 and 6/96
- there is no permanent structural damage to the central fovea
- the lesion size is less than or equal to 12-disc areas in greatest linear dimension
- there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity (VA) changes

no → NICE criteria do not apply – Pathway not applicable

yes → **Treatment options (choose least expensive suitable treatment):**
Bevacizumab or ranibizumab biosimilar (TA 155) – **see note 1,2**
Aflibercept (TA 294) – **see note 1,2**
Brolucizumab (TA 672) – **see note 1,2**
Faricimab (TA 800) – **see note 1,2**
Box 1

After **loading dose (3 x monthly injections bevacizumab, ranibizumab, aflibercept and brolucizumab; 4 x monthly injections faricimab)**, is there an adequate response (i.e. improvement/stabilisation in VA and reduction in signs of disease activity (also see **note 2** concerning adverse events)

yes → **Continue treatment until maximum VA is achieved and/or there are no signs of disease activity. Ensure ongoing monitoring and assessment of adequate response to treatment.** (See also **note 2** concerning adverse events)
Bevacizumab[1,2] or Ranibizumab biosimilar[3,4]: Continue monthly, or if possible, treat-and-extend (by 2 weekly increments - up to 12 weekly)**.**
When disease appears stable (VA stable and no disease activity), consider suspending treatment and monitor[7]. (see **note 4**)
Aflibercept[5]: 4th Injection 8 weeks after last injection, thereafter, if possible treat-and-extend (by 2-4 weekly increments – up to 16 weekly)**.** When disease appears stable, (VA stable and no disease activity), consider suspending treatment and monitor[5]. (see **note 4**)
Brolucizumab[6]: Assess disease activity at 16 weeks: for eyes with persistent disease (based on VA, OCT imaging and symptoms), continue on 8 weekly interval. For eyes with inactive disease, the treatment interval may be extended to 12 weekly. Treatment intervals may further be individualised based on disease activity**.** When disease appears stable, (VA stable and no disease activity) consider suspending treatment and monitor[7]. (see **note 4**)
Faricimab[9]: Assess disease activity at 20 and/or 24 weeks: for eyes with persistent disease (based on VA, OCT imaging and symptoms), continue on 8 weekly interval. For eyes with inactive disease, the treatment interval may be extended to 12 weekly. Treatment intervals may further be individualised based on disease activity. When disease appears stable, (VA stable and no disease activity) consider suspending treatment and monitor[7]. (see **note 4**)
Box 2

no → **Primary suboptimal response****
Consider switch to alternative anti-VEGF (go to **Box1) (see note 3)**
**disease activity as assessed by VA and anatomical parameters
OR
Continue with existing anti-VEGF, (go to **Box 2**)
NB a total of two switches is allowed per eye

no → **Primary non-response - no prospect of functional improvement**
Discontinue treatment (**see note 4)**

Has disease stability been achieved?

yes → Box 2

no → **Reduce dosing intervals:**
Bevacizumab[1,2] or Ranibizumab[3]: reduce dosing interval (max 1 injection/month)
Aflibercept[5]: reduce dosing interval (max 1 injection/month)
Brolucizumab[6]: reduce dosing interval (max 1 injection/2months)
Faricimab[9] reduce dosing interval (max 1 injection/2months)

Has disease stability been achieved?

yes → Box 2

no → Suboptimal response despite optimal treatment or frequent number of injections required (4-6 weekly) and switching may reduce the number injections/appointments?

yes → Consider switch to alternative anti-VEGF (**go to Box1**) (see **note 3**)
OR
Continue with existing anti-VEGF if alternatives already trialled.
Only continue where an adequate response is maintained.

NB a total of two switches is allowed per eye

Permanent discontinuation of anti-VEGF treatment[7]
Consider stopping anti-VEGF treatment if the eye develops severe, progressive loss of visual acuity despite treatment as recommended. **(See note 5)**

Stop anti-VEGF treatment if the eye develops late AMD (wet inactive) with no prospect of functional improvement

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Note 1: If there is more than one treatment available, NICE recommends a discussion between the responsible clinician and the patient about the advantages and disadvantages of each treatment (considering therapeutic need and likely adherence to treatment). If more than one treatment option is suitable, the least expensive will be chosen (taking into account; administration costs, dosage and price per dose).
Consider using bevacizumab or ranibizumab biosimilar first line. If using bevacizumab as unlicensed this must be discussed and recorded.

Note 2 Anti VEGF adverse events; Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. There is limited data on safety in the treatment of patients with prior history of stroke or transient ischaemic attacks or myocardial infarction within the last 6 months[13,4] *See individual SPC's for other adverse events and further prescribing information.*
Brolucizumab may cause intra-ocular inflammation[4]. Due to this, it is not suitable for remote clinics, initial bilateral administration, patients with a previous history of uveitis, vision in only eye or history or vein occlusion. Patients must receive information and be counselled on the adverse effects of brolucizumab (to be documented in the patient notes). Clinical staff must exclude history of prior intra-ocular inflammation and should use a red flag questionnaire after each injection to identify signs and symptoms of intra-ocular inflammation. Patients with positive symptomatology would then be further screened with slit-lamp examination supported with widefield retinal imaging if deemed appropriate. Further brolucizumab treatment should be withheld in cases with retinal vasculitis/vascular occlusion.
Local agreement; the pathway allows for a switch to alternative anti VEGF if first anti VEGF had to be stopped due to an adverse event (either before efficacy could be assessed (i.e. before 3 consecutive monthly injections) or in patients who are responding to first anti VEGF treatment)

Note 3: **Sequential anti-VEGF treatment: Local agreement;** For patients with suboptimal response, maximum two anti-VEGF switches per eye are included in the pathway. Sequential anti-VEGF treatment in the same eye is not commissioned for non-responders.
Evidence for switching is limited.[1,2,3,4,5]
NICE guideline 82 states '*Consider switching anti-VEGF treatment for people with late AMD (wet active) if there are practical reasons for doing so (for example, if a different medicine can be given in a regimen the person prefers) but be aware that clinical benefits are likely to be limited*'.[5] When switching anti-VEGF, reloading may not be required unless there is a significant break in treatment.[6] Patients can revert back to previous treatment option if desired outcomes of a switch are not achieved.

1.Gale RP *et al. Anatomical and functional outcomes following switching from aflibercept to ranibizumab in neovascular age-related maculardegeneration in Europe:* SAFARI study. Br J Ophthalmol 2019; 0:1-7
2.Barthelmes D *et al.* Effects of switching from ranibizumab to aflibercept in eyes with exudative age-related macular degeneration. Br J Ophthalmol 2016; 0: 1-6
3.Mantel I *et al.* Switching between ranbizumab and aflibercept for the treatment of neovascular age-related macular degeneration. Survey or Ophthalmology 2018; 63:638-645
4.Bulisch L et al., 'Short-term real-world outcomes following intravitreal brolucizumab for neovascular AMD: SHIFT study', Br J Ophthalmol 2021;0:1–7
5.Age related macular degeneration, Nice guideline 82, published 23rd January 2018
6.Local clinical expertise
(adapted form Proposed SWL Drug Pathway Wet Age-related Macular Degeneration (not published – draft only available)

Note 4: Stable disease – consider observation without giving anti-VEGF treatment if the disease appears stable[7]
- Advise people with late AMD (dry), or people with AMD who have been discharged from hospital eye services to: self-monitor their AMD, consult their eye-care professional as soon as possible if their vision changes, continue to attend routine sight-tests with their community optometrist.
- Self-monitoring: Discuss self-monitoring with people with AMD and explain the strategies available. Advise people with AMD to report any new symptoms or changes in the following to their eye-care professional as soon as possible (such as blurred or grey patch in their vision, straight lines appearing distorted, objects appearing smaller than normal). Encourage and support people with AMD who may lack confidence to self-monitor their symptoms. If people are not able to self-manage their AMD, discuss AMD monitoring techniques with their family members or carers (as appropriate)

Note 5: permanent stopping criteria[8]
- BCVA in the eye to be treated is less than 15 letters absolute on 2 consecutive visits, attributable to AMD, in the absence of other pathology
- Reduction in BCVA of 30 letters or more compared to either baseline and/or best recorded level since baseline as this may indicate lack of responsiveness to treatment, or adverse event or both
- There is a hypersensitivity reaction to treatment (established or suspected)
- Lesion morphology has deteriorated while on optimum treatment

References:

1. Shienbaum G et al., 'Bevacizumab for neovascular age related macular degeneration using a treat and extend regimen: clinical and economic impact.' https://www.sciencedirect.com/science/article/abs/pii/S0002939411006362
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3. www.medicines.org.uk Lucentis 10 mg/ml solution for injection in pre-filled syringe accessed via https://www.medicines.org.uk/emc/product/5418/smpc 28/05/2021.
4. Amoaky W. et al., 'Initiation and maintenance of a Treat-and-Extend regimen for ranibizumab therapy in wet age related macular degeneration: recommendations from the UK Retinal Outcomes Group, Clinical Ophthalmology 2018:12 1731–1740
5. www.medicines.org.uk Eylea 40 mg/ml solution for injection accessed via https://www.medicines.org.uk/emc/product/2879/smpc 28/05/2021
6. www.medicines.org.uk Beovu 120mg/ml solution for injection accessed via https://www.medicines.org.uk/emc/product/11145 28/05/2021

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7. Age related macular degeneration, NICE guideline 82, published 23rd January 2018 (accessed 28/5/2021)
(NB: published prior to brolucizumab launch in the UK)
8. The Royal college of ophthalmologists, age-related macular degeneration- guidelines for management, September 2013
9. www.medicines.org.uk Vabysmo 120 mg/mL solution for injection accessed via https://www.medicines.org.uk/emc/product/13741 17/10/22

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