South West London
Wet Age-related Macular Degeneration (wet AMD) Drug Pathway
Version 2.1

Contents:

Approved by: SWL Integrated Medicines Optimisation Committee
Date: 18/12/2024

SWL Drug Pathway - Wet Age-related Macular Degeneration Drug Pathway: High Cost Drug Pathway

Version 2.1 (based on NICE with local adaptations)

Do **all** of the following apply:
- Best corrected visual acuity (VA) is between 6/12 and 6/96
- No permanent structural damage to central fovea
- Lesion size ≤ 12 disc areas in greatest linear dimension
- Evidence of recent presumed disease progression (blood vessel growth, as indicated by FA, or recent VA changes)

No → Does patient have late active wet-AMD and VA ≥ 6/12 (note 11)?

Yes → Consider early treatment with Bevacizumab - load with 3 monthly injections, thereafter PRN/ treat and extend (note 10)

No – Continue to monitor/ Consider discharge

Yes →

Loading phase: monthly injections

1st choice: Ranibizumab biosimilar ▼ (TA155) (note 1,2,8)
2nd choice: Aflibercept (TA294) (note 1,3,8) **OR**
Bevacizumab (TA1022) (notes 1, 4, 8) **OR**
Faricimab (TA800) (note 1, 5, 8) **OR**
3rd choice: Brolucizumab ▼ (TA672) (note 1,6,8)

Suboptimal Primary response:
- Consider switch to alternative anti-VEGF (with or without reloading) (note 7) **OR**
- Continue with existing anti-VEGF

No ↑

Is there a response (i.e. improvement/stabilisation in VA **and** reduction in signs of disease activity)?

Yes ↓

4th and 5th injection:
Ranibizumab biosimilar: 4th injection treat-and extend (if no disease activity) or continue monthly (if disease activity)
Aflibercept: 4th injection 2 months after last injection then, treat-and-extend (if no disease activity) or continue 2-monthly (if disease activity)
Bevacizumab: 4th injection every month until maximum visual acuity and/or there are no signs of disease activity. Thereafter individualise treatment intervals based on disease activity.
Faricimab: 5th injection treat and extend (if no disease activity), or every 8-12 weeks (if disease activity)
Brolucizumab: 4th injection every 2 months after last injection (if disease activity) or every 3 months (if no disease activity)

Has patient improved (i.e. OCT fluid decreased **and** VA increased/stabilised)?

Yes ↓ / No →

Continue treatment – Reduce dose interval:
Ranibizumab biosimilar: no more than 1 injection/month
Aflibercept: no more than 1 injection/2 months (note 3)
Bevacizumab: no more than 1 injection/month
Faricimab: no more than 1 injection/ 21 days (note 5)
Brolucizumab: no more than 1 injection/2 months

Disease stability achieved? (No →)

Yes ↓

Disease stability achieved?

Yes → **Treat and extend -** Increments of:
Ranibizumab biosimilar: 2 weeks (up to 1 injection/12 weeks used in studies)
Aflibercept: 2-4 weeks (up to 1 injection/4 months used in studies)
Bevacizumab: Individualise treatment intervals based on disease activity
Faricimab: 4 weeks (up to 1 injection/16 weeks)
Brolucizumab: Increase dose interval (up to 1 injection/3 months used in studies)
➔When VA stable and OCT dry: consider suspending treatment and monitor

No ↓

- Is response sub-optimal in the first year of treatment (i.e. after ≥ 6 ranibizumab / bevacizumab injections (given at monthly intervals) or ≥5 aflibercept / faricimab / brolucizumab injections)? (note 6) **or**
- Is response deteriorating in long term users who are now heavy users? (note 7)
- Are frequent (monthly) injections required to maintain disease stability? (note 7)

Yes ↓

Suboptimal response:
- Consider switch to alternative anti-VEGF (with or without reloading) (note 7) **OR**
- Continue with existing anti-VEGF

NOTE: Max 4 switches (between 3 anti-VEGFs) per eye

Annual review at 12 months:
Has patient responded adequately to treatment and qualifies for further treatment as per locally modified RCO criteria (Sept 2013)) (note 9) i.e.:
- BCVA in treated eye is ≥15 letters absolute on 2 consecutive visits (unless vision of <15 letters is attributable to other pathology)
- BCVA has not reduced by ≥30 letters from baseline and/or best recorded level since baseline (with allowance for those with only one seeing eye)
- Lesion morphology has not deteriorated while on optimum treatment
- No hypersensitivity reaction to treatment (confirmed or suspected)

Yes ↑ / No →

Have 4 switches/eye been exhausted?

No ↑ / Yes ↓

Is VA <6/96 and overall vision is expected to benefit from ongoing treatment (e.g. only seeing eye)?

Yes → Discontinue licensed anti-VEGF; consider Bevacizumab (NG82) (note 10)

No ↓

Discontinue high cost drug treatment (note 11) or if atypical wet AMD suspected (e.g. Idiopathic Polypoidal Choiroidal Vasculopathy (IPCV)) refer to a tertiary centre for review

SWL Drug Pathway - Wet Age-related Macular Degeneration Drug Pathway: Notes

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Clinicians and commissioners should refer to the relevant technology appraisal and SPC for each drug for further information about eligibility and prescription

Note 1 – Drug Choice: If there is more than one NICE approved 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) unless an order of preference is stated in the TAs.
As agreed by the SWL Ophthalmology Medicines Optimisation Network, clinicians are advised to consider history of uveitis/systemic disorders associated with uveitis, vision in other eye, treatment in one or both eyes, patient consent. Where clinically appropriate, ranibizumab biosimilar should be considered as a 1st choice. Due to rare but serious side effects reported in clinical trials, SWL recommend brolucizumab as a 3rd choice option. It can be considered for treatment naïve eyes if there is a good clinical reason to justify use over ranibizumab/ aflibercept / bevacizumab / faricimab.

Note 2 – Ranibizumab: One injection/month until max visual acuity (VA) is achieved and/or no signs of disease activity i.e. no change in VA and in other signs and symptoms of the disease under continued treatment (3 or more monthly injections may be needed). Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by VA and/or anatomical parameters. For treat-and-extend regimen, once max VA is achieved and/or no signs of disease activity, treatment intervals can be extended stepwise by up to 2 weeks at a time until signs of disease activity or visual impairment recur. Limited data on bilateral use of ranibizumab (including same-day administration) do not suggest an increased risk of systemic adverse events compared with unilateral treatment.[7,8] Up to 1 injection/12 weeks has been used in studies.[13-15]
SWL commission max 12 injections/year.

Note 3 – Aflibercept: One injection/month for 3 consecutive doses, followed by 1 injection every 2 months. Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at two months or further extended using a treat-and-extend dosing regimen, where injection intervals are increased in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly to a minimum of two months during the first 12 months of treatment. There is no requirement for monitoring between injections. Based on the physician's judgement the schedule of monitoring visits may be more frequent than the injection visits. Treatment intervals greater than four months between injections have not been studied. The safety and efficacy of aflibercept administered to both eyes concurrently have not been systematically studied. If bilateral treatment is performed at the same time this could lead to an increased systemic exposure, which could increase the risk of systemic adverse events.[10] Aflibercept may be preferred for: vitrectomised eyes/requiring victrectomy[17,18] (due to long half-life[15]).
SWL commission max 8 injections in year 1 and max 6 injections in subsequent years.

Note 4 – Bevacizumab (Lytenava® - licensed for intravitreal use): One injection/4 weeks (monthly) until maximum visual acuity is achieved and/or there are no signs of disease activity, i.e., no change in visual acuity or in other signs and symptoms of the disease under continued treatment. The kinetics of bevacizumab gamma efficacy indicate that three or more consecutive monthly injections may be needed initially. Thereafter, the healthcare professional may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. Monitoring and treatment intervals should then be determined by the healthcare professional and should be based on disease activity, including clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography). If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, the medicinal product should be discontinued. The safety and efficacy of bevacizumab gamma administered in both eyes concurrently have not been studied. If bilateral treatment is performed at the same time, this could lead to an increased potential for adverse events, both ocular and systemic due to increased exposure. [12]
SWL commission max 12 injections/year.

Note 5 – Faricimab: One injection/4 weeks for first 4 doses. Thereafter, use a treat-and-extend approach following an assessment of the individual patient's anatomic and visual outcomes. The dosing interval may be extended up to every 16 weeks, and extensions in increments of up to 4 weeks should be considered, based on the physician's judgement of the individual patient's anatomic and/or visual outcomes. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reductions of up to 8 weeks may be implemented if deemed necessary. Treatment intervals shorter than 21 days between injections have not been studied.[9]
Currently SWL commission max 8 injections in year 1 and max 7 injections in subsequent years (subject to review).

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Note 6 – Brolucizumab : One injection/month for first 3 doses. Treatment intervals may then be individualised based on disease activity as assessed by visual acuity and/or anatomical parameters suggested at 16 weeks (4 months) after treatment start. If no disease activity, consider treatment every 12 weeks (3 months). If disease activity, consider treatment every 8 weeks (2 months). Treatment intervals may be further individualised based on disease activity. The safety and efficacy of brolucizumab administered in both eyes concurrently have not been studied.[11] Intra-ocular inflammation and ocular occlusive events were reported more frequently with brolucizumab than aflibercept (EMA requested close post-marketing monitoring).[19, 20]

SWL commission max 8 injections in year 1 and max 6 injections in subsequent years.

Note 7 – Sequential Anti-VEGF Treatment: For patients with suboptimal response, SWL commission maximum four anti-VEGF switches per eye as specified in the pathway:

- Early switch (after 3 loading doses)
- Switchback in the first year of treatment
- Long-term users with diminishing response despite frequent re-treatments[21, 22, 23, 24]
- Long term heavy users who require frequent (e.g. monthly) ranibizumab injections to maintain disease stability.[16]

Sequential anti-VEGF treatment in the same eye is not commissioned for non-responders.

When switching anti-VEGF, reloading may not be required unless there is a significant break in treatment.[16]

There is limited uncontrolled evidence for switching between ranibizumab and aflibercept[21, 22, 23, 24] and for switching between brolucizumab[25] or faricimab[26, 27] and other anti-VEGFs, but NICE acknowledges this practice.[1,5] Clinical consensus considered it reasonable to allow a switch from another anti-VEGF to brolucizumab and vice versa.[16] All is subject to review in line with evidence.

Note 8 – 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.[10] See SPC for other adverse events.

If clinically appropriate, SWL commission ONE 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 9 – Cataract: Patients scheduled for a cataract operation within the next 3 months and if it is anticipated that vision will improve so that locally modified RCO discontinuation criteria no longer apply, may continue treatment.

Note 10 – Bevacizumab (not licensed for intravitreal use): If approved through Trust governance processes, bevacizumab may be considered after discussion of treatment options as suggested by NICE Guideline 82[1]:

- In eyes with visual acuity of 6/96 or worse, consider anti-VEGF treatment for late AMD (wet active) only if a benefit in the person's overall visual function is expected (e.g. if the affected eye is the better-seeing eye).
  - Suggested dose: *prn*[16] or treat and extend regime[30]
- Anti-VEGF treatment for eyes with late AMD (wet active) and visual acuity better than 6/12 is clinically effective and may be cost effective depending on the regimen used.
  - Suggested dose: 3 x monthly injections then *prn*[16] or treat and extend regime[30]

This is supported by Court of Appeal upholding the lawfulness of NHS bevacizumab choice policy for wet AMD patients.[28]

SWL commission max 12 injections/year.

Note 11 – IFR: Funding requests for treatment outside this commissioned pathway can be made via the Individual Funding Request (IFR) process to the relevant commissioning organisation (see swlimo.southwestlondon.icb.nhs.uk for IFR policy and application form).

SWL Drug Pathway – Wet Age-related Macular Degeneration Drug Pathway: Drug Information for Advanced Therapies

Version 2.1 (this list is not exhaustive; see summary of product characteristics (SPC) for full information)

Drug Class	Drug Name	Administration	Contra-indications	Special warnings and precautions	
Anti VEGF	Ranibizumab (0.5mg) Aflibercept (2mg) Faricimab (6mg) Brolucizumab (6mg) Bevacizumab (1.25mg, Lytenava®)	Intravitreal route	• Ocular or peri-ocular infection • Severe intra-ocular inflammation • Signs of irreversible ischaemic visual function loss in patients with retina vein occlusion • Hypersensitivity to the active substance or to any of the excipients	• Females of childbearing potential to use effective contraception during treatment and for at least 3 months after last dose • Glaucoma (poorly controlled; do not use while intra-ocular pressure is ≥30 mmHg) • Intra-ocular surgery within the previous or next 28 days • Retinal detachment or macular hole (discontinue treatment if rhegmatogenous retinal detachment, retinal break, or stage 3 or 4 macular holes develop, until repaired) • Risk factors for retinal pigment epithelial tear • Treatment-related decrease in best corrected visual acuity (BCVA) of ≥30 letters compared with last assessment	• History of myocardial infarction, stroke, TIAs • Aneurysm and artery dissection in patients with or without hypertension • Any modifiable risk factors (such as smoking and hypertension) should be reduced as much as possible. Patients should be monitored and treated for hypertension as required. • Active systemic infection • Diabetic macular oedema due to type 1 diabetes (limited information available) • Diabetic patients with HbA1c over 12% (limited information available) • Previous intravitreal injections • Arterial thromboembolic events and non-ocular haemorrhage • **Brolucizumab only:** intraocular inflammation and retinal vascular occlusive events occurred more frequently in the brolucizumab 3mg and 6mg groups than with the comparator 2mg aflibercept
Anti VEGF	Bevacizumab (unlicensed)	Intravitreal route	• Hypersensitivity to the active substance or to any of the excipients • Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies. • Pregnancy	• Taken from IV route of administration; unable to ascertain frequency or severity when administered via intravitreal route • Females of childbearing potential should use effective contraception during treatment and for at least 6 months after last treatment • Osteonecrosis of the jaw • History of cardiovascular disease and uncontrolled hypertension (increased risk of cardiovascular events, especially in the elderly) • History of hypertension (increased risk of proteinuria—discontinue if nephrotic syndrome) • Aneurysm and artery dissection in patients with or without hypertension	• Increased risk of haemorrhage • Increased risk of tumour-associated haemorrhage • Intra-abdominal inflammation (risk of gastro-intestinal perforation and gall bladder perforation) • Risk factors for arterial thromboembolism • Untreated CNS metastases • Increased risk of fistulas (discontinue permanently if tracheo-oesophageal or grade 4 fistula develops) • Elective surgery (withhold treatment and avoid for at least 28 days after major surgery or until wound fully healed)

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1. NICE Guideline 82 (NG82), Age-related macular degeneration. 23 January 2018
2. NICE TA155: Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. 27 August 2008
3. NICE TA800: Faricimab for treating wet age-related macular degeneration . 29 June 2022
4. NICE TA294: Aflibercept solution for injection for treating wet age-related macular degeneration. 24 July 2013
5. NICE TA672: Brolucizumab for treating wet age-related macular degeneration (including NICE resource impact report). 3 February 2021
6. NICE TA1022: Bevacizumab gamma for treating wet age-related macular degeneration. 4 December 2024
7. Lucentis® (ranibizumab) Summary of Product Characteristics (SPC) https://www.medicines.org.uk/emc/product/307 Accessed 16/03/2023; last updated 28/12/2022
8. Ongavia® (ranibizumab) Summary of Product Characteristics (SPC) https://www.medicines.org.uk/emc/product/13885 Accessed 16/03/2023; last updated 11/07/2022
9. Vabysmo® (faricimab) Summary of Product Characteristics (SPC) https://www.medicines.org.uk/emc/product/13741 Accessed 16/03/2023; last updated 22/12/2022
10. Eylea® (aflibercept) Summary of Product Characteristics (SPC) https://www.medicines.org.uk/emc/product/2879 Accessed 16/03/2023; last updated 14/12/2022
11. Beovu® (brolucizumab) Summary of Product Characteristics (SPC) https://www.medicines.org.uk/emc/product/11145 Accessed 16/03/23; last updated 05/05/22
12. Lytenava® (bevacizumab) Summary of Product Characteristics (SPC) https://products.mhra.gov.uk/product/?product=LYTENAVA%2025%20MG%2FML%20SOLUTION%20FOR%20INJECTION Accessed 04/12/24; last updated 27/09/24
13. Berk K *et al.* Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. Ophthalmol 2015;122(1):146-152
14. Regillo CD *et al.* Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol. 2008;145(2):239-248
15. Schmidt-Erfurth U *et al. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. O*phthalmol 2011;118(5):831-839
16. Local clinical expertise
17. Jung JJ *et al.* Aflibercept anti-vascular endothelial growth factor therapy in vitrectomized eyes with neovascular age-related macular degeneration. Acae Ophthalmol 2016;94(3):e249-e250
18. Schmidt-Erfurth U *et al.* Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). Br J Ophthalmol 2014;98(9):1144-1167
19. Monés J *et al.* Risk of inflammation, retinal vasculitis, and retinal occlusion- related events with brolucizumab- Post hoc review of HAWK and Harrier. Ophthalmol 2020: 1-10
20. The European Medicines Agency (EMA) European Public Assessment report. Brolucizumab (Beovu®). 12 12.19, EMEA/H/C/004913/000. www.ema.Europa.eu
21. Gale RP *et al. Anatomical and functional outcomes following switching from aflibercept to ranibizumab in neovascular age-related macular degeneration in Europe:* SAFARI study. Br J Ophthalmol 2019;0:1-7
22. 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
23. Mantel I *et al.* Switching between ranbizumab and aflibercept for the treatment of neovascular age-related macular degeneration. Survey of Ophthalmology 2018;63:638-645
24. Kioke N *et al. Results of switchback from ranibizumab to aflibercept in patients with exudative age-related macular degeneration. Clin Ophthalmol* 2019;13:1247-1251
25. Baumal CR, *et* al. Efficacy and safety of brolucizumab in age-related macular degeneration: A systematic review of real-world studies. *Acta Ophthalmol* 2023;101(2):123-139
26. Rush RB, *et al*. Intravitreal Faricimab for Aflibercept-Resistant Neovascular Age-Related Macular Degeneration. Clin Ophthalmol. 2022 Dec 9;16:4041-4046
27. Ali F, *et al*. V. Real-world use of Faricimab: From the IRIS® Registry. Presented at the Hawaiian Eye and Retina 14-20 January 2023
28. https://www.landmarkchambers.co.uk/court-of-appeal-upholds-lawfulness-of-nhs-avastin-choice-policy-for-wet-amd-patients
29. NHS England Operational note: updated commissioning recommendations for medical retinal vascular medicines following the national procurement for ranibizumab biosimilars. 24 July 2023
30. The Royal College of Ophthalmologists Commissioning Guidance: Age related macular degeneration service. June 2021

SWL Drug Pathway - Wet Age-related Macular Degeneration Drug Pathway: Version control

Version 2.1 (based on NICE with local adaptations)

Version number	Main amendments	Approval date
0	NICE TA155 and TA294	24 July 2013
1.0	Include approved recommendations from South West London Ophthalmology Medicines Optimisation network meeting (13th March 2020 and 24th March 2021) including: • Local agreement on drug choices • Local agreement on sequential treatment and switching between treatments • Incorporate treat and extend strategy • Include bevacizumab for patients falling outside anti-VEGF NICE criteria • Include safety advice for brolucizumab	15 Dec 2021
2.0	• Add faricimab (NICE TA800) • Add drug information for advanced therapies • Update format	20 Mar 2024
2.1	• Add bevacizumab (Lytenava®) (NICE TA1022) • Update new Note 4 to include bevacizumab dosing and monitoring information	18 Dec 2024
Date of next review: 18 Dec 2026 (or earlier if indicated)		