Briefing Paper for Surrey Heartlands Integrated Care System (ICS) Area Prescribing Committee (APC)

Wet Age-Related Macular Degeneration (wet AMD)
Sequential use of anti-VEGF treatments

Situation

Sequential Use

NHS Surrey Heartlands CCG does not currently have a policy for switching between the intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatments, for treatment failure/treatment insufficiency.

This has been recommended by the Royal College of Ophthalmologists since 2014, and by neighbouring CCGs. This has not been previously recommended to the APC as there is very little evidence of benefit, but with a new product on the market, brolucizumab, which promises to have a longer duration of action than the well established medicines, but for which there are safety concerns, there is a need to allow this to be used as a third line treatment, and this is reflected in the NICE costing template for brolucizumab.

It is also now understood that there may be the need to escalate doses from larger intervals achieved to monthly injections if the underlying condition deteriorates. At the moment, only ranibizumab is approved for monthly injections, and therefore there may be the need to switch to ranibizumab.

The Area Prescribing Committee will be asked to:

- Approve the increased access to THREE switches for existing NICE approved anti-VEGF treatments to optimise response
- Agree table below (Page 7)

Background

What is Wet age-related macular degeneration:

Wet age-related macular degeneration (AMD) develops when abnormal blood vessels grow into the macula. These leak blood or fluid which leads to scarring of the macula and rapid loss of central vision. **https://www.macularsociety.org/macular-disease/macular-conditions/wet-age-related-macular-degeneration/**

How is it treated:

Wet AMD can be treated if caught early. Drugs are injected into the eye to stop the growth of the abnormal blood vessels which leak and therefore create a wet macula. Following diagnosis people will usually have a loading dose of three injections, once a month for three months.

A patient will then be assessed to see if more injections are required immediately or

whether treatment can be paused, and the condition monitored. If ongoing treatment is required, the interval between the injections can usually be increased gradually to find the best balance between injection frequency and the degree of exudative disease activity, such as retinal fluid and haemorrhage. This is known as 'treat and extend'.

NICE Technology Appraisals www.nice.org.uk

There are currently 3 intravitreal licensed anti-vascular endothelial growth factor (anti-VEGF) treatments recommended by the National Institute for Health & Care Excellence (NICE).

- Ranibizumab TA155 (May 2012)
- Aflibercept TA294 (July 2013)
- Brolucizumab TA671 (Feb 2021)

NICE Technology Appraisal recommendations:
All the following circumstances apply in the eye to be treated:

- the best-corrected visual acuity (BCVA) 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 changes)

Brolucizumab NICE TA 671 (February 2021)
https://www.nice.org.uk/guidance/ta672/resources
Switching between anti-VEGF treatments is not specifically discussed in the NICE TA, however in the resource template, NICE assumption for England is that

- *'If 5% of people in the prevalent population currently on aflibercept or ranibizumab switch to brolucizumab this would be around 13,000 people in year 1 and 9,000 people in year 5, there is uncertainty around the number of people who will switch so this is left for local input in the template'.*

Switching and stopping antiangiogenic treatment for late AMD
Switching is recommended in NICE CG82 (Jan 2018) as follows

1.5.15 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.

This guideline also recognises the place in therapy of the off-label use of Bevacizumab within NICE thresholds. Surrey Heartlands APC has previously agreed to fund this treatment subject to individual providers taking this decision within their internal governance processes.

What does professional society guidance say?
The Royal College of Ophthalmologists (RCOphth) published guidelines for the management of age-related macular degeneration in 2013. This includes criteria for considering discontinuation of treatment permanently.

Following the publication of NICE TA294 on aflibercept in 2013, the RCOphth released a college statement (2014) supporting switching between anti-VEGF agents, citing that NICE do not list prior treatment with anti-VEGFs as an exclusion to further treatment for either ranibizumab or aflibercept. They also specify circumstances when the use of a second anti-VEGF agent should be considered.

Assessment

National guidance and priorities

- NICE technology appraisals are available for the 3 licensed anti-VEGF treatments (ranibizumab, aflibercept & brolucizumab), and the NICE guidance recognises the off-label use of bevacizumab. Each of these treatments are treatment options for the treatment of wet AMD and are currently funded on a routine basis by the high-cost drugs team.

Clinical Effectiveness

- The evidence for switching to improve efficacy is weak, however taking into consideration that there is benefit in treatment until complete failure, there will be minimal cost implication for switching rather than continuing with the same product. In addition, this will provide the confidence to clinicians in trying the newer products
- The NICE Technology appraisal for brolucizumab indicates that this could reduce the number of injections required per year. In the trials, brolucizumab was compared to regular aflibercept injections (2 monthly), whereas in practice aflibercept is mostly used in a treat and extend protocol which reduces the number of injections per year. Which may reduce the calculated reduced cost as calculated in the NICE technology appraisal.
- However, clinicians are currently concerned about the risk of vasculitis with brolucizumab. The ophthalmology network agreed that the main place in therapy for brolucizumab is for patients currently receiving frequent doses of the well- established treatments (ranibizumab & aflibercept), but where attempts to extend dose intervals has not worked in this group of patients, the feedback is that at this point the potential benefits of brolucizumab probably outweigh the risks and should be considered with informed consent. Once there is more real like experience the confidence in using brolucizumab may increase
- Allowing switching at this point will facilitate the introduction of the ranibizumab biosimilar. At that point, an additional switch will be requested to APC specifically for the purpose of switching to a biosimilar. The Surrey Heartlands Ophthalmology Medicine Network (Retina) will consider this when more information about the biosimilars are known.

Patient Safety

- Safety outcomes were reported in one meta-analysis (brolucizumab not included) In general, no additional increase in safety concerns were demonstrated upon switching between anti-VEGF agents and rates of systemic and local side effects were considered rare in incidence.
- Brolucizumab trials demonstrated an increased risk of vasculitis which treated promptly may avoid blindness. The NICE TA recognises this risk but suggest that the risk is no greater than that for the alternative treatments.
- The clinicians in Surrey Heartlands and South West London are not reassured by the NICE statement on safety and wish to restrict the place in therapy of

brolucizumab to last line unless there is a specific patient request for earlier treatment, which is within their rights as per NICE guidance.

Patient factors

- Switching to another agent may enable the patient to gain some sight and stop/slow down the growth of the abnormal blood vessels in the affected eye/eyes.
- Switching between agents is not routinely available at this time which means that some patients are being treated and may be having a suboptimal response to treatment.
- With the recent approval of brolucizumab and the imminent arrival of biosimilar ranibizumab, it will be beneficial to patients and to the health economy to fund switching of anti-VEGF therapies to enable the use of the most cost effective first line treatment(s) with confidence that this will not affect patients' access to treatments for which there is a very long experience.
- The aim of treatment is not only to maximise visual acuity but to minimise the number of visits to the clinic and the number of injections required.

Environmental impact

- None known
- Fewer injections = reduced carbon footprint

Equality & diversity

- Wet AMD is usually diagnosed in patients over 50 years of age
- Feedback from clinicians is that people with darker pigmentation of the eyes appear to respond better to aflibercept than ranibizumab.

Place in therapy relative to available treatments

Currently routine funding is available to
Switch from ranibizumab to aflibercept (blueteq forms are available)

- to enable intravitreal injections every 8 weeks (not for treatment failure)
- to reduce the patient footfall during covid

- There is currently no routine funding available for switching between the other agents.
- Sequential use of other high-cost drug treatments (recommended by NICE) are routinely funded for all other specialities
- Request to allow THREE switches per eye (currently) as per the switching table (Page 7).

Stakeholder views

- Wide consultation with ophthalmology specialist colleagues who are all in agreement with this proposal.

Cost-effectiveness

- See below for information

Recommended traffic light status:

- Red Traffic light status
- Payment by Results excluded medicine
- Blueteq forms will be used by ophthalmology specialist teams for initiation and

continuation

Routine funding in other CCGs

- **South West London** – Allow switching of anti-VEGF up to FOUR switches per eye. This decision is taking implementation of biosimilar ranibizumab into account.
- **NHS Sussex Commissioners** – Allows switching between the anti-VEGF treatments if NICE guidance is met, there is no specific switching policy in place
- **Kent & Medway** –. Allow switching of anti-VEGF up to TWO switches per eye Brolucizumab has been reserved as the last treatment option when all else has failed, but there is still an opportunity to preserve vision.

Financial implications/risks

Patient Numbers:
Information from invoices received by the CCG

Year	Product	Number of episodes (may include treatment in both eyes for one patient)	Cost invoiced to CCG
2019/20	Aflibercept	5836	£3,473,447
	Ranibizumab	1559	£838,027
2021/22	Aflibercept	9287	£3,441,953
	Ranibizumab	4015	£1,890,658
	Brolucizumab	12	£5,904

The costs of aflibercept and ranibizumab dropped from April 2020 (aflibercept 13% & ranibizumab 10%).
The cost of the anti-VEGF treatments were comparable until May 2021 when the cost of ranibizumab was increased by Novartis

As previously discussed for other specialities using high-cost drugs, the financial implications of funding switching is difficult to assess but the following points should be noted:

- Currently treatments may be continued sub-optimally as switching is currently not funded. All licensed treatments are similarly priced and switching at this point will not create a cost pressure and may improve outcomes for patients.
- Agreeing to increase the number of switches will give clinicians confidence to start new patients on the biosimilar because there will be options to switch to another agent in cases of suboptimal response. The resulting increased use of biosimilar ranibizumab will result in savings.
- Only one biosimilar ranibizumab is expected imminently and we are waiting

for information about increased competition. It is possible that this one biosimilar cost reduction may be less than more recent entry of biosimilars into the market. It is for this reason that the authors are not currently including strong plans for biosimilar implementation until launch. Members of the ophthalmology medicines network are committed to maximise savings to the NHS within the constraints of maintaining patient safety.

Summary

- Evidence for switching is weak because it was not in the interest of the drug companies to carry out this research and is unlikely that the difference is very large.
- It is possible that the changing of the anti-VEGF molecule (switching) will reduce the wetness and/or allow for the increase of intervals between injections. The alternative is not to stop current treatment but to continue until the eyesight is lost (6/96)
- Anti-VEGF treatments tend to dry the retina which prevents the development of blindness. The longer the retina remains dry, the slower the progression to blindness and the lower the injection frequency.
- This proposal would bring us in line with our neighbouring CCGs. With a view to adding another switch (in line with SWL) when we plan to implement biosimilar ranibizumab.

Recommendations

The Area Prescribing Committee will be asked to:

1. Approve the increased access to THREE switches for existing NICE approved anti-VEGF treatments to optimise response
2. Agree table below (Page 7)

Prepared by: Clare Johns (Lead Commissioning Technician – Pharmaceutical Commissioning (Surrey Heartlands CCG) & Carina Joanes (Lead Commissioning Pharmacist – Pharmaceutical Commissioning)

Declaration of Interest: None

Date: May 2022

Reviewed by:

Declaration of Interest: None

Date:

VERSION CONTROL SHEET

SELECTION TABLE

Best Correct Visual Acuity (BCVA) within NICE thresholds (6/12 to 6/96)		
1st switch	***2nd switch***	***3rd switch***
Ranibizumab *(Treat and extend)*	***Aflibercept*** *(Treat and extend)*	***Brolucizumab****
Aflibercept *(Treat and extend)* *(Provide reason for 1st line use in tick box form)*	***Ranibizumab*** *(Treat and extend)* ***OR*** ***Brolucizumab****	***Ranibizumab*** *(Treat and extend)* ***OR*** ***Brolucizumab****
Brolucizumab*	***Ranibizumab OR Aflibercept*** *(Treat and extend)*	***Ranibizumab OR Aflibercept*** *(Treat and extend)*

Back to the top

* The Surrey Heartlands Medicines Management Ophthalmology Clinical Network identified that full safety profile for brolucizumab has not been completely understood, especially with regards to the incidence and severity of vasculitis. The network therefore recommended that informed consent describing the risks was obtained and recorded whenever brolucizumab is prescribed.

Glossary

Treat and extend –

- Dependant on response to treatment. Extend treatment interval e.g. 4 weekly injections to 6 weekly injections