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Norfolk and Waveney Integrated Care System

DIABETIC MACULAR OEDEMA PATHWAY 2023

Norfolk and Waveney Integrated Care System

1. Table of Contents

2. Document Control Sheet

Name of document:	Diabetic macular oedema pathway 2023
Description of policy	N&WICB high-cost drug pathway for DMO
Version	1.0
Scope	
Prepared by	Medicine optimisation team With input/advice from specialists at NNUH, QEH & JPH
Impact Assessment (Equalities and Environmental)	
Other relevant approved documents	
Evidence base / Legislation	Level of Evidence: ~~A. based on national research-based evidence and is considered best evidence~~ **B. mix of national and local consensus** ~~C. based on local good practice and consensus in the absence of national research based information.~~
Dissemination	Is there any reason why any part of this document should not be available on the public web site? ~~Yes~~ / **No**
Approved by	N&WICB Therapeutics advisory group
Authorised by	N&WICB Therapeutics advisory group
Review date and by whom	June 2025
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2.1 Revision History

Revision Date	Summary of changes	Author(s)	Version Number
05/09/2022	First draft of pathway	A. Charlwood, M. Sully	0.1
17/02/2023	Inclusion of Faricimab, and local specialist recommendations	As above & local specialist input	0.2
07/03/2023	Added potential option for switching to be considered by TAG. Added summary document.	As above	0.3
07/06/2023	Approved by TAG	As above	1.0

2.2 Approvals

This document requires the following approvals either individual(s), group(s) or board.

Name	Title	Date of Issue	Version Number
Norfolk & Waveney ICB Therapeutics Advisory Group		07/06/2023	1.0

2.3 Introduction

2.4 Relevant NICE technology Appraisals

Technology Appraisal*	Title
TA274	Ranibizumab for treating diabetic macular oedema
TA301	Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy
TA346	Aflibercept for treating diabetic macular oedema
TA349	Dexamethasone intravitreal implant for treating diabetic macular oedema
TA613	Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy
TA799	Faricimab for treating diabetic macular oedema
TA820	Brolucizumab for treating diabetic macular oedema
TA824	Dexamethasone intravitreal implant for treating diabetic macular oedema

*NICE recommendations **also apply to biosimilar products of the technologies** that have a marketing authorisation, allowing the use of the biosimilar for the same indication.

2.5 Pathway scope

This pathway, using up to date published NICE Technology Appraisals (Tas) and evidenced based medicine, is a guide to the initiation and maintenance of high-cost drugs in the management of diabetic macular oedema (DMO).

The pathways include biologic agents:

- Anti-VEGFs (Aflibercept, Ranibizumab)
- Anti-VEGF & Ang-2 (Faricimab)
- Corticosteroid implants (Dexamethasone, Fluocinolone)

Drugs should be used in accordance with the relevant TA. The links are included in this document. Inclusion will be allowed for any new high-cost drugs that are approved by NICE prior to review of the pathway, provided that the relevant local "New Medicines" Policy and process has been followed. Those drugs should be used in accordance with the relevant NICE TA. The NICE recommendations also apply to biosimilar drugs, where marketing authorisations allow use of the biosimilar for the indication specified in the relevant NICE TA.

2.6 Classification

DMO is the accumulation of excess fluid in the extracellular space within the retina in the macular area, typically in the inner nuclear, outer plexiform, Henle's fibre layer, and subretinal space[1,2].

3. When to use anti-VEGF treatment

Anti-VEGF treatment for visual impairment caused by DMO are recommended for use based on the criteria specified in NICE TA274 for Ranibizumab, NICE TA346 for Aflibercept and NICE TA799 for Faricimab. If anti-VEGF treatment is deemed unsuitable, consider a corticosteroid intravitreal implant.

3.1 Inclusion criteria

✓ Vision impairment caused by DMO
✓ the eye has a central retinal thickness of 400 micrometres or more at the start of treatment

3.2 Exclusion criteria

✗ Hypersensitivity to the active substances or excipients

- ✗ Active/suspected ocular/periocular infections
- ✗ Significant ocular inflammation
- ✗ Patient has had TIA/Stroke since last 3 months
- ✗ Pregnancy

4. Monitoring

4.1 Baseline Monitoring

Through following assessments be completed:

- Visual Acuity (VA)
- OCT: Note CRT at starting and subsequent visits
- FFA: Comment on macular perfusion and peripheral features
- Lens status: Phakic/Pseudophakic
- IOP: Baseline record
- No active PDR or very severe ischaemic NPDR
    - If active PDR or very severe ischaemic NPDR: Arrange PRP laser

4.2 Routine Monitoring

- Both eyes should be assessed at monitoring appointments.
    - OCT – should be the primary diagnostic indicator.
    - VA
- Routine IOP testing post injection is not recommended but annual IOP monitoring is required to identify sustained IOP rise from repeated injections.

5. Choice of Anti-VEGF

As per NICE guidelines, when using biologics, choose the least expensive treatment. Take account of administration costs, dosage, price per dose and commercial arrangements. NHS England recommendations are that:

"Clinicians should consider ranibizumab biosimilar where this is clinically appropriate and there is capacity to do so. If ranibizumab biosimilar is contraindicated or not clinically appropriate for the specific patient then, subject to the criteria specified in the relevant NICE technology appraisal guidance, clinicians should then consider aflibercept or faricimab, dexamethasone or fluocinolone."[3]

5.1 Ranibizumab dosing interval[4]

- Offer monthly injections for three months, reassess, and if needed continue with monthly intervals
    - Improvement measured as improvement in VA by at least 5 letters and CMT reduction from baseline after 3 months of treatment.
    - Maintain monthly injections until maximum VA & minimal CRT on 3 consecutive visits then suspend treatment
- Once achieved, either
    - Discontinue treatment, and initiate monthly follow up visits and initiate retreatment after recurrent disease activity (oedema on retinal OCT scan and/or drop in vision) has occurred
        - The "when required" regime has the disadvantage of only treating disease after it has caused a deterioration (in vision or retinal swelling) and requiring frequent review visits (1 monthly) putting a burden on the patient and clinic and cost to the CCG. It also often results in patients having to return on a separate day for retreatment (2-stop service)
    - Treat and extend regime
        - There is limited evidence supporting T&E in DMO management and long-term cost effectiveness. The T&E regime is commissioned subject to regular review and annual monitoring of efficacy and costs.

5.1.1 Ranibizumab treat and extend protocol

- Increase the treatment intervals by 2/52 between each injection until a maximum interval of 12/52

- If CRT or VA worsens, signs of recurrence on OCT or VA loss (5 letters or more), reduce treatment interval by 2/52 and monitor

5.2 Aflibercept dosing interval [5]

- Treatment to be commenced with 1 injection every month for 5 months followed by injections every 2 months. After 3rd & 5th injection review the following:
  - Success:
    - BCVA improved >5 letters and no fluid
    - VA & CRT. If VA has improved and no fluid on OCT (CRT <300 micron) – defer treatment
    - Go to year 2 schedule
  - Improving:
    - VA has improved by >5 letters
    - CRT has improved by >10%.
    - Continue with treatment schedule.
- 2nd Year Aflibercept Schedule
  - Review and recommence treatment as required (see when to recommence treatment) ***or***
  - Follow treat and extend protocol.

5.2.1 Aflibercept treat and extend protocol

- For treat-and-extend regimens, treatment interval may be increased by 2-4 weeks every successive visit (up to maximum inter-treatment interval of 16 weeks) unless signs of activity or decrease in VA are noted where interval may be reduced to no less than 4-weekly.
  - Trial without treatment may be considered when no disease activity or VA reduction are noted on three consecutive visits at 16-week treatment interval

5.2.2 "When required" treatment recommencement criteria

✓ VA reduces by ≥5 letters from BCVA ***or***
✓ CRT increases ≥10% from best achieved

It is the responsibility of the team to make sure patient is seen in the clinic every 3 months to assess the status of the diabetic retinopathy in the treating eye and the contralateral eye.

5.3 Faricimab dosing interval[6]

- Offer 4-weekly injections for first 4 doses
  - Treatment may be individualised using a treat-and-extend approach following an assessment of the individual patient's anatomic and visual outcomes.
  - The dosing interval may be extended from every 4 to every 16 weeks, with extensions in increments of up to 4 weeks, 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

6. Discontinuation of Anti-VEGF

✗ Adverse reaction to medication
✗ No improvement or worsening of VA

6.1 Switching Anti-VEGF therapy – TO BE COMMISSIONED

As per NHS England's commissioning recommendations:

"For patients with suboptimal response, clinicians should consider changing to **alternative anti-VEGF**. If initial treatment selected was ranibizumab biosimilar, clinicians should consider changing to either aflibercept or faricimab, dexamethasone or fluocinolone."

1. Patients requiring more than 8 injections of ranibizumab, or aflibercept, in the last 12 months can change to another treatment if considered appropriate
2. Intolerance to ranibizumab or aflibercept - It is appropriate to change to the other treatment using the following definition of intolerance:
    a. Persistent sub-retinal or intra-retinal fluid on several consecutive occasions despite repeated intravitreal injections **OR**
    b. Continued use is unsuitable because of an allergic response, where there is still potential for improvement in vision with further treatment.
3. Inadequate response
    a. It is appropriate to switch treatment if there has been insufficient clinical benefit after optimum treatment, and the treating clinician believes switching may yield a better response.
4. Deteriorating response in long term users
    - … who develop drug tolerance over time.
    - …. with prior sub-optimal response to Aflibercept and Ranibizumab.

7. When to use intravitreal corticosteroid implants

Although there are no specific recommendations locally which set criteria for switching from Anti-VEGF treatment to corticosteroid implants, collaborative trust guidelines published in the BMJ suggest:

"Our guideline adopted a definition for insufficient response that included '<20% reduction in CRT and <5 letters gained'"

For further context and detailed information:

Treatment choices for diabetic macular oedema: a guideline for when to consider an intravitreal corticosteroid, including adaptations for the COVID-19 era

7.1 Dexamethasone intravitreal implants

7.1.1 Consider use if

✓ DMO still present post laser treatment ***or***
✓ Leaking microaneurysms at edge of foveal avascular zone which cannot be treated by laser

7.1.2 Inclusion criteria

✓ DMO has not responded well enough to, or if they cannot have non-corticosteroid therapy.

7.1.3 Exclusion criteria

× Hypersensitivity to the active substance or to any of the excipients
× Active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
× Advanced glaucoma which cannot be adequately controlled by medicinal products alone.
× Aphakic eyes with ruptured posterior lens capsule.
× Eyes with Anterior Chamber Intraocular Lens (ACIOL), iris or transscleral fixated intraocular lens and ruptured posterior lens capsule

7.1.4 Dosing interval

- Monitor & retreat every 6 months
- Normally one implant would be expected to last 6 months. The SPC advises up to 7 implants may be used and that only one implant per patient is recommended.
    - If required more frequently than 6 monthly, or a total of more than 7, submit as individual funding request (IFR).

7.2 Fluocinolone acetonide intravitreal implant

7.2.1 Consider use if

✓ Treating chronic DMO that is insufficiently responsive to available therapies in an eye with a natural lens (phakic eye).

7.2.2 Inclusion criteria

✓ Insufficient response to prior treatment with laser photocoagulation or other available therapies for diabetic macular oedema
✓ Affected eye is phakic

7.2.3 Exclusion criteria

- The implant is to be used in an eye with an intraocular (pseudophakic) lens
- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.
- Infectious uveitis.

7.2.4 Dosing interval

- Each implant releases fluocinolone acetonide for up to 36 months
- An additional implant may be administered after 12 months if the patient experiences decreased vision or an increase in retinal thickness secondary to recurrent or worsening diabetic macular oedema.
    - Retreatments should not be administered unless the potential benefits outweigh the risks.
    - Any patient requiring a total of 3 or more implants require an individual funding request (IFR).

8. Interchangeability

As per MHRA guidelines:

"Once authorised, **a biosimilar product is considered to be interchangeable with their [reference product (RP)]**, which means a prescriber can choose the biosimilar medicine over the RP (or vice versa) and expect to achieve the same therapeutic effect**. Likewise, a biosimilar product is considered to be interchangeable with another biosimilar to the same RP**.

As a result of interchangeability, switching patients from one product to another (RP or biosimilar) has become clinical practice. The decision rests with the prescriber in consultation with the patient, in line with the principles of shared decision making; both need to be aware of the brand name of the product received."[2]

9. Pregnancy

There is limited data for safety of biologic medicines in pregnancy and breastfeeding. The decision to continue biologic medicines throughout pregnancy must be individualised. This should consider the various therapies, severity of the mother's health prior to therapy, risk of a disease flare if therapy is discontinued, and the impact of a disease flare on the mother and unborn child. This should be discussed by a multi-disciplinary team. Patients who discontinue treatment during pregnancy should resume biological therapy as soon as possible following delivery.

9.1 Choice of therapy for patients planning to conceive

See the table below for further details on specific biologics in the different stages of pregnancy, information collated from the BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding[7], and SPC of the relevant biologic.

	Compatible with trimester		
Drug	1st	2nd	3rd
Ranibizumab	No, use effective contraceptive during treatment.		
Aflibercept	No, use effective contraceptive during treatment.		
Faricimab	No, use effective contraceptive during treatment.		
Brolucizumab	No, use effective contraceptive during treatment.		
Dexamethasone	No, use effective contraceptive during treatment.		
Fluocinolone	No, use effective contraceptive during treatment.		

9.2 Breastfeeding

There is little information available regarding the excretion of biologics in breast milk. Immunoglobulins are excreted in human breast milk, so a risk to a child cannot always be ruled out. The decision to breastfeed or continue/discontinue therapy should consider both the benefits of breastfeeding to the infant and the benefits of therapy to the mother.

See the table below for further details on specific biologics in breastfeeding, information is taken from the SPC of the relevant biologic. Where no data or recommendation is provided, it would be appropriate to use the "Time to stop treatment prior to surgery" listed in section 11 to determine time between discontinuing treatment and starting breastfeeding.

Biologic	Compatible with Breastfeeding
Ranibizumab	No data – not recommended
Aflibercept	No data – not recommended
Faricimab	No data – not recommended
Brolucizumab	No data – not recommended
Dexamethasone	No data – not recommended
Fluocinolone	No data – not recommended

10. Correspondence

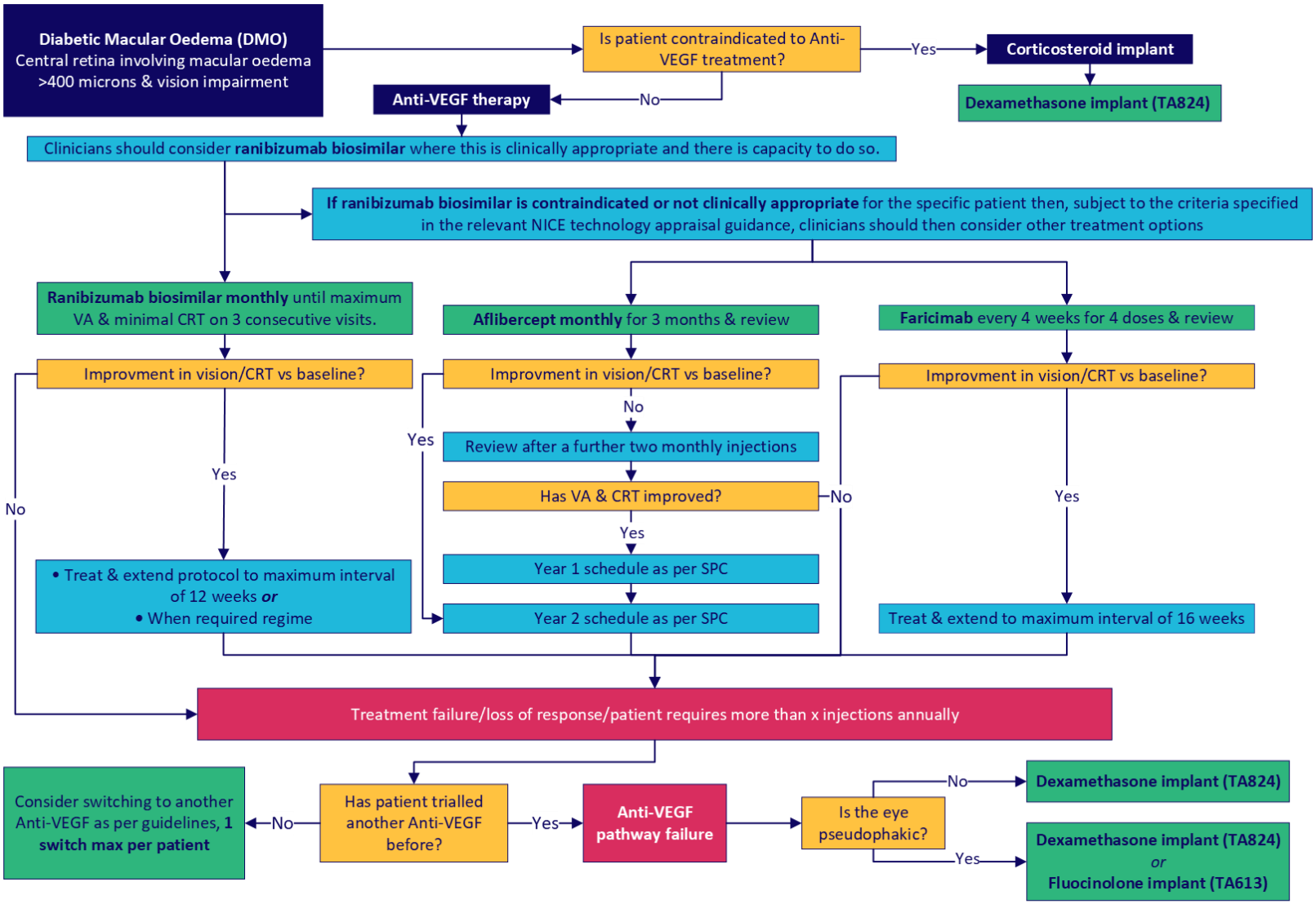
10.1 Information to be included in correspondence from secondary to primary care:

- Main diagnosis/diagnoses
- Date(s) of intervention
- Secondary diagnosis/diagnoses
- Date of last examination, with findings & timing of next planned review/ contact with secondary care
- Current medical therapy including any previous treatments within pathway (including non-biologics)
- Recommended length of current medical therapy

10.2 Information to be included in correspondence from primary to secondary care:

- Date last prescription issued
- All current and recent medications.
- Functional impact e.g., impact on employment, family, and social functioning
- Any newly diagnosed co-morbidities

11. Appendix 1 – DMO flowchart



12. Appendix 2: Summary of commisioining position document

DMO commissioning summary

1. Available treatment options
Anti-VEGF: **Ranibizumab**, **Aflibercept**, **Faricimab** & **Brolucizumab** (not included in algorithm due to local clinical preferences)
Steroid implant: **Dexamethasone** (phakic/pseudophakic) & **Fluocinolone** (pseudophakic)

2. Preferred first line use
Ranibizumab biosimilar should be considered as the first line option where clinically appropriate

3. Treatment regimen: Ranibizumab
Offer monthly injections for three months, reassess, if needed continue with monthly intervals. Improvement measured as improvement in VA by at least 5 letters and CMT reduction from baseline after 3 months of treatment. Maintain monthly injections until maximum VA & minimal CRT on 3 consecutive visits then suspend treatment

3. Treatment regimen: Aflibercept
Treatment to be commenced with 1 injection every month for 5 months followed by injections every 2 months. After 3rd & 5th injection review, skip to year 2 schedule if appropriate (see pathway for details), otherwise complete year 1 as per SPC. In year 2 review/recommence treatment as required or follow treat and extend protocol.

3. Treatment regimen: Faricimab
Offer 4-weekly injections for first 4 doses. Treatment may be individualised using a treat-and-extend approach following an assessment of the patient's anatomic and visual outcomes. Dosing interval may be extended from 4 to 16 weeks, in increments of up to 4. 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

3. Treatment regimen: Brolucizumab
1 injection every 6 weeks for the first 5 doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered.

3. High frequency switching guidelines
If a patient is requiring more than the following doses per year:

Biologic	Year 1 annual injections	Year 2 onwards	Y2 dosing interval
Ranibizumab	8	8	≥7 weeks
Aflibercept	8	8	≥7 weeks
Faricimab	6	4	≥13 weeks

Consider switching to a different Anti-VEGF in pathway. If patient has sub-optimal response to the new Anti-VEGF, a switch back is commissioned.

4. Maximum treatments commissioned – Steroid implants
Note: Administration to both eyes concurrently is not recommended. Retreatment may be performed.
Dexamethasone intravitreal implant (phakic or pseudophakic eye):
- If required more frequently than 6 monthly, or a total of more than 7, submit as individual funding request (IFR).

Fluocinolone acetonide intravitreal implant (pseudophakic eye):
- Any patient requiring a total of 3 or more implants require an individual funding request (IFR)

5. Switching options for patients – TO BE COMMISIONED
One switch to another Anti-VEGF is commissioned within pathway after failure with 1 Anti-VEGF. After 2 failures with Anti-VEGF treatment a steroid implant should be used. If clinician is switching due to high frequency usage, then a switch back to the original Anti-VEGF is commissioned.

Switching from steroid implants to Anti-VEGF is not commissioned.

13. Appendix 3: – NICE technology appraisal detail

TA274	Ranibizumab for treating diabetic macular oedema 1. Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if: 1.1. the eye has a central retinal thickness of 400 micrometres or more at the start of treatment **and** 1.2. the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of this appraisal. 2. People currently receiving ranibizumab for treating visual impairment due to diabetic macular oedema whose disease does not meet the criteria in 1 should be able to continue treatment until they and their clinician consider it appropriate to stop.
TA301	Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy 1. Fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies only if: 1.1. the implant is to be used in an eye with an intraocular (pseudophakic) lens and 1.2. the manufacturer provides fluocinolone acetonide intravitreal implant with the discount agreed in the patient access scheme.
TA346	Aflibercept for treating diabetic macular oedema 1. Aflibercept solution for injection is recommended as an option for treating visual impairment caused by diabetic macular oedema only if: 1.1. the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and 1.2. the company provides aflibercept with the discount agreed in the patient access scheme. 2. People whose treatment with aflibercept is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue aflibercept until they and their NHS clinician consider it appropriate to stop.
TA349	Dexamethasone intravitreal implant for treating diabetic macular oedema 1. Dexamethasone intravitreal implant is recommended as an option for treating diabetic macular oedema only if: 1.1. the implant is to be used in an eye with an intraocular (pseudophakic) lens and 1.2. the diabetic macular oedema does not respond to non-corticosteroid treatment, or such treatment is unsuitable. 2. People whose treatment with dexamethasone intravitreal implant was started within the NHS before this guidance was published but is not recommended for them by NICE in this guidance, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
TA613	Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy 1. Fluocinolone acetonide intravitreal implant is not recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies in an eye with a natural lens (phakic eye). 2. This recommendation is not intended to affect treatment with fluocinolone acetonide intravitreal implant that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

TA799	Faricimab for treating diabetic macular oedema 1. Faricimab is recommended as an option for treating visual impairment due to diabetic macular oedema in adults, only if: 1.1. the eye has a central retinal thickness of 400 micrometres or more at the start of treatment 1.2. the company provides faricimab according to the commercial arrangement. 2. If patients and their clinicians consider faricimab to be 1 of a range of suitable treatments (including aflibercept and ranibizumab), choose the least expensive treatment. Take account of administration costs, dosage, price per dose and commercial arrangements. 3. These recommendations are not intended to affect treatment with faricimab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.
TA820	Brolucizumab for treating diabetic macular oedema 1. Brolucizumab is recommended as an option for treating visual impairment due to diabetic macular oedema in adults, only if: 1.1. the eye has a central retinal thickness of 400 micrometres or more at the start of treatment 1.2. the company provides brolucizumab according to the commercial arrangement. 2. If patients and their clinicians consider brolucizumab to be 1 of a range of suitable first-line treatments (including aflibercept and ranibizumab), choose the least expensive treatment. Take account of administration costs, dosage, price per dose and commercial arrangements. 3. These recommendations are not intended to affect treatment with brolucizumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.
TA824	Dexamethasone intravitreal implant for treating diabetic macular oedema 1. Dexamethasone intravitreal implant is recommended as an option for treating visual impairment caused by diabetic macular oedema in adults only if their condition has not responded well enough to, or if they cannot have non-corticosteroid therapy. 2. This recommendation is not intended to affect treatment with dexamethasone intravitreal implant that was started in the NHS before this guidance was published. Adults having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.