Macular Drugs Pathways

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Produced by GMSS. Lead author: Anna Pracz, Advanced Medicines Optimisation Pharmacist.
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## DOCUMENT CONTROL

**Revision history and approvals**

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<thead>
<tr>
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<tbody>
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</tr>
</tbody>
</table>

**Distribution**

Final version available on GMMMG website.
<table>
<thead>
<tr>
<th>Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Macular Drugs Pathways</td>
<td>4</td>
</tr>
<tr>
<td>2. Concurrent drug use, safety, and other advice</td>
<td>5</td>
</tr>
<tr>
<td>3. Neovascular (wet) age related macular degeneration</td>
<td>6</td>
</tr>
<tr>
<td>4. Diabetic macular oedema</td>
<td>7</td>
</tr>
<tr>
<td>5. Macular oedema secondary to central retinal vein occlusion</td>
<td>8</td>
</tr>
<tr>
<td>6. Macular oedema secondary to branch retinal vein occlusion</td>
<td>9</td>
</tr>
<tr>
<td>7. Choroidal neovascularisation associated with pathological myopia</td>
<td>10</td>
</tr>
<tr>
<td>8. Vitreomacular traction</td>
<td>10</td>
</tr>
<tr>
<td>8. References</td>
<td>11</td>
</tr>
</tbody>
</table>
Macular Drugs Pathways

1. The purpose of this document is to enable consolidation of the approach towards the use of ophthalmic high cost drugs across Greater Manchester inclusive of independent providers.

2. The guidance focuses on drug use and related issues and entry criteria for treatment. Service models, referral pathways and diagnostics are not discussed as they vary across the region. Non-drug interventions, disease prevention and paediatric use are outside of the remit of this document.

3. The responsible commissioner will not normally fund any treatment where the patient does not meet the agreed criteria as outlined in this document. The use of drugs not on this pathway is not normally commissioned. Drug treatment outside of the outlined pathway will be considered only in exceptional circumstances and will need prior approval via the individual funding request route. People currently receiving their treatment prior to the implementation of this guidance, should be able to continue the treatment until they and their NHS clinician consider it appropriate to stop.

4. In case a treatment for one of the aforementioned conditions is needed following a clinical trial, the responsibility for ongoing funding remains with the treatment provider or a pharmaceutical company.

5. All high cost drugs used for treatment of the aforementioned conditions including free of charge supply or drugs with a discounted price (e.g. obtained via the patient access scheme) should be recorded in a transparent manner and made available to commissioners in order to enable monitoring of appropriateness of use and spend.

6. Blueteq forms which comply with these pathways are available. Where Blueteq has been introduced to the trust as part of the contractual arrangements, funding approval for the PbR excluded high cost drugs will be made by meeting the accepted criteria outlined on completion and submission of a Blueteq form.
Notes on systemic effects of anti-VEGFs
There is a theoretical risk of systemic arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of anti-VEGFs. Patients with prior history of myocardial infarction, stroke or transient ischaemic attack should be counselled appropriately.

Note on ocular side effects of steroids
Use of intraocular corticosteroids may induce cataracts, sustained increased intraocular pressure (normally manageable), or steroid induced glaucoma, which in rare cases may require surgery.

Ocriplasmin and transient sight deterioration
There is a risk for a significant, but transient loss of visual acuity during the first week after the injection.

For more details refer to summary of products characteristics for each drug available at: www.medicines.org.uk

Concomitant (concurrent) use of intraocular drugs - the bilateral use of the same or two different drugs in each eye.

Often, both eyes are affected by the same disease. However, the disease affecting each eye may be at a different stage, and so can vary in presentation and response to treatment. Patients may also present with different diseases affecting each eye.

Bilateral drug treatment is justifiable in such cases, including use of different drugs in each eye. Patients should be made aware of the usual cumulative risks of concomitant injections to each eye.

Where the same drug is administered to both eyes, separate vials of drug and separate sets of instruments should be used for each eye.

For more details on concurrent use, other special warnings, and contraindications refer to summary of products characteristics for each drug available at: www.medicines.org.uk

Combination use of drugs – the use of more than one drug in the same eye. Such use of ophthalmic drugs is outside of this pathway and is not normally commissioned.

Sequential treatment – the use of a subsequent drug within a group of drugs with the same action, or a drug with a different mode of action, if there is insufficient response with the first treatment. Sequential treatment, where relevant, is discussed under each disease.

General post-administration advice
Post operative discharge antibiotics (to take home) are not recommended with the exception of prophylaxis after procedures involving larger bore injections (e.g. dexamethasone or fluocinolone).

Patients should be advised to report any signs of infection and inflammation without delay and instructed to report any symptoms such as pain, increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision or increased sensitivity to light.

Notes on concurrent drug use

Glossary

PAS – patient access scheme
MO – macular oedema
VA – visual acuity
IOP – intraocular pressure
CMT – central macular thickness
CNV – choroidal neovascularisation
PM – pathological myopia
RCOphth – The Royal College of Ophthalmologists
1. Neovascular age related macular degeneration (wet AMD)

Age related macular degeneration is a progressive, irreversible disease causing loss of central vision. The majority of people are affected by dry (atrophic) AMD which has a gradual and chronic presentation. The neovascular form, or wet AMD, accounts for 10% of all cases of AMD, but about 60% of those are considered advanced at presentation. Progression of wet AMD varies from a few months to three years. If left untreated, the diagnosis is poor with a significant visual loss (6/60 or worse) occurring within two to three years.

In the UK, the prevalence of wet AMD in people over 65 years old is nearly 5% and increases to over 12% in those over 80 years old. The risk of wet AMD developing in the fellow eye is 12% at one year and 27% at four years, and approximately 50% of patients within five years.

Evidence shows that early detection and treatment allow preventing further disease progression. Treatment with anti-VEGFs will only improve vision in a third of patients. The majority will maintain vision and about 10% will not respond to initial therapy.

### Ranibizumab

**Initiation:** one intravitreal injection monthly until maximum VA is achieved and/or there are no signs of disease activity. Usually 3 or more consecutive monthly injections may be needed. Minimum interval between injections in the same eye is 4 weeks.

**Continuation:** one injection monthly. Monitoring and treatment intervals should be determined by the physician. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques.

For treat-and-extend regimen, once maximum VA is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than 2 weeks at a time. Treatment may be continued for as long as there is visual benefit.

**Discontinuation:** when visual and anatomic parameters indicate that the patient is not benefiting from continued treatment.

For temporary discontinuation (drug withholding) refer to product literature and RCOphth guidance.

### Aflibercept

**Initiation:** one intravitreal injection per month for 3 consecutive doses. Minimum interval between injections in the same eye is 4 weeks.

**Continuation:** one injection every two months. There is no requirement for monitoring between injections. After the first 12 month of treatment, and based on visual and/or anatomic outcomes, the treatment interval may be extended.

For treat-and-extend regimen, the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The schedule of monitoring should be determined by treating physicians and may be more frequent than injection schedule. Treatment may be continued for as long as there is visual benefit.

**Discontinuation:** when visual and anatomic parameters indicate that the patient is not benefiting from continued treatment.

For temporary discontinuation (drug withholding) refer to product literature and RCOphth guidance.

### Sequential treatment:

The use of a second anti-VEGF agent should be considered when:

- a particular anti-VEGF drug has not shown clinical benefit after optimum treatment, or
- where continued use of the initial anti-VEGF agent is unsuitable for example because of an allergic response or uveitis
- and where there is still potential for improvement in vision, or improved stabilisation at 6/96 or better, with further treatment.

Where patients are refractory to therapy with anti-VEGFs, the possibility of other diagnoses, such as idiopathic polypoidal choroidopathy and central serous chorioretinopathy should be considered. For details on investigation and management follow RCOphth advice.

For the advice on bilateral, concurrent and combination use of ophthalmic drugs, safety information and glossary see page 2.
2. Diabetic macular oedema (DMO)

**1st line - anti-VEGF**

- **Ranibizumab** NICE TA274 or **Aflibercept** NICE TA346

The drug must be provided with the discount agreed in relevant PAS and the following criterion must be met:
- the central retina thickness is 400 micrometres or more when treatment is started.

- **Initiation**: one intravitreal injection monthly until maximum VA is achieved and/or there are no signs of disease activity. Usually 3 or more consecutive monthly injections may be needed. Minimum interval between injections in the same eye is 4 weeks.

- **Continuation**: one injection monthly. Monitoring and treatment intervals should be determined by the physician. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques. For treat-and-extend regimen, once maximum VA is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval may be extended by up to one month at a time.

- **Discontinuation**: when visual and anatomic parameters indicate that the patient is not benefiting from continued treatment. For temporary discontinuation (drug withholding) refer to product literature and RCOphth guidance.

- **Where there is an insufficient response or loss of efficacy after initial response in use of 1st anti-VEGF, consider use of 2nd anti-VEGF before moving on to second line intravitreal steroid.**

**2nd line (if no improvement with previous therapy) - steroid implant**

- **Dexamethasone** NICE TA349 or **Fluocinolone** NICE TA301

The following criteria must be met:
- it is to be used in an eye with a pseudophakic (artificial) lens
- and the DMO has not improved with non-corticosteroid treatment, or such treatment was not suitable.

- Single intravitreal implant, but may be repeated after approximately 6 months if initially effective, and there is decreased vision, with or without increase in retinal thickness, secondary to recurrent or worsening diabetic macular oedema. Monitor regularly for IOP. Currently, there is no experience of the efficacy or safety of repeated treatment with dexamethasone in DMO beyond 7 implants.

- **Note**: indicated for chronic macular oedema only.

- Single intravitreal implant releases fluocinolone 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 DMO. Retreatment should not be administered unless the benefits outweigh the risks. Monitoring for IOP at least quarterly. NB Not licensed for first line use. Contraindicated in pre-existing glaucoma.

For the advice on bilateral, concurrent and combination use of ophthalmic drugs, safety information and glossary see page 2.
3. Macular oedema secondary to central retinal vein occlusion (CRVO)

**Ranibizumab**
NICE TA283
Must be supplied via PAS.

**Aflibercept**
NICE TA305
Must be supplied via PAS.

**Dexamethasone**
NICE TA229
Use of steroid may be preferred in patients with recent history of cardiovascular events and those who do not favour monthly injections.

Treatment with an anti-VEGF may be preferred in eyes with a previous history of glaucoma and younger patients who are phakic.

**Initiation**: one intravitreal injection monthly until maximum VA is achieved and/or there are no signs of disease activity. Usually 3 or more consecutive monthly injections may be needed. Minimum interval between injections in the same eye is 4 weeks.

**Continuation**: where VA stability is achieved for 3 consecutive months, monitor monthly and resume when monitoring indicates loss of VA due to MO secondary to CRVO. Restart monthly injections until stable VA is reached for 3 consecutive months (minimum 2 injections). Monitor at follow up visits including VA, macular thickness, IOP and assess presence of neovascularisation at angle and iris. Treatment intervals may be gradually extended depending on patient’s response. If disease activity recurs, the treatment interval should be shortened accordingly.

**Discontinuation**: consider stopping if after 3 consecutive monthly treatments, VA has not improved and CMT has not reduced from baseline. Note that reduction in retinal oedema with stable VA may be considered as satisfactory although suboptimal outcome. Stop, if after six consecutive monthly treatments, VA has not improved and CMT has not reduced from baseline.

**Sequential treatment**
A switch to another anti-VEGF once the first one lost efficacy may be considered and 3 consecutive monthly injections should be considered to assess efficacy.

A switch from steroid to anti-VEGF and vice versa may be considered if the first intervention ceased to be effective.

Retinal vein occlusions (RVOs) are a common cause of visual acuity loss in the UK. Both types of RVO can be classified into ischaemic and non-ischaemic. CRVO results from blockage of the central retinal vein. If left untreated, only a small proportion of patients with CRVO spontaneously improve over time. Non-ischaemic CRVO may resolve completely; however, 30% of non-ischaemic CRVO can turn into ischaemic.

In general, CRVO generally worsens over time and 75% of people with CRVO will develop macular oedema within two months of diagnosis and all patient with MO will experience visual impairment. Visual impairment is more common in patients with CRVO than BRVO. Over 90% of patients with ischaemic CRVO have a final VA of 6/60 or worse. Most patients are affected unilaterally. Under 10% of CRVO are bilateral at presentation. The fellow eye involvement over a year period is about 5%.
4. Macular oedema secondary to branch retinal vein occlusion (BRVO)

**Dexamethasone**  
NICE TA229

**or**

**Ranibizumab**  
NICE TA283

**or**

**Aflibercept**  
NICE TA409

One the following criteria must be met:
- treatment with laser photocoagulation has not been beneficial, or
- laser photocoagulation is not suitable because of the extent of macular haemorrhage.

Steroid my be preferred in patients with recent history of cardiovascular event and those who do not favour monthly injections.

**Single intravitreal implant**, but may be repeated after 4 - 6 months, when patient initially experienced response to treatment followed subsequently by a loss in VA, until visual stability is obtained. NB product license does not specify retreatment interval and advises there is little evidence on re-administration less often than 6 monthly and beyond 2 implants in RVO. More frequent and repeated treatments can increase risk of adverse effects and should be considered and discussed with the patient. Monitor regularly for IOP and formation or progression of cataract.

Patients who experience and retain improved vision should not be retreated.

Patients who experience deterioration in vision, which is not slowed by treatment with dexamethasone should not be retreated.

**Initiation**: one intravitreal injection monthly until maximum VA is achieved and/or there are no signs of disease activity. Usually 3 or more consecutive monthly injections may be needed. Minimum interval between injections in the same eye is 4 weeks.

**Continuation**: where VA stability achieved for 3 consecutive months, monitor monthly and resume when monitoring indicates loss of VA due to MO secondary to BRVO. Restart monthly injections until stable VA is reached for 3 consecutive months (minimum 2 injections). Monitor at follow up visits including VA, macular thickness, IOP and assess presence of neovascularisation at angle and iris. Treatment intervals may be gradually extended depending on patient’s response. If disease activity recurs, the treatment interval should be shortened accordingly.

**Discontinuation**: consider stopping if after 3 consecutive monthly treatments, VA has not improved and CMT has not reduced from baseline. Note that reduction in retinal oedema with stable VA may be considered as satisfactory although suboptimal outcome. Stop, if after six consecutive monthly treatments, VA has not improved and CMT has not reduced from baseline.

**Sequential treatment**
A switch to another anti-VEGF once the first one lost efficacy may be considered and 3 consecutive monthly injections should be considered to assess efficacy. A switch from steroid to anti-VEGF and vice versa may be considered if the first intervention ceased to be effective.

**Aflibercept**

NICE TA409 allows use of aflibercept without prior laser therapy. It needs to be noted that for some patients laser photocoagulation may be useful and considered as initial treatment of BRVO. For further directions refer to local algorithms and RCOphth guidance.

**Retinal vein occlusions (RVOs)** are common cause of visual acuity loss in the UK. Both types of RVO can be classified into ischaemic and non-ischaemic. BRVO is 2-6 times more common than CRVO. Although more patients with BRVO than CRVO develop macular oedema within two months of diagnosis, less patients experience visual deterioration due to MO (50%). The prognosis of BRVO is better than CRVO as 50-60% of untreated patients retain a 6/12 or better visual acuity after one year. However, many patients do not present immediately and early treatment may be required. The majority of BRVO present as a unilateral condition. About 5% of patients present with bilateral BRVO at diagnosis, and up to 10% patients develop bilateral disease over time.
5. Choroidal neovascularisation associated with pathological myopia

Choroidal neovascularization (CNV) is one of the most important vision-threatening complications of pathologic myopia and occurs in 5–10% of myopic patients (up to 3% of general population), with a positive correlation between risk and degree of myopia. Among myopic patients with pre-existing CNV, more than 30% will develop CNV in the fellow eye within 8 years. Without treatment, the long-term prognosis of myopic CNV is poor; approximately 90% of patients will have a VA of 6/60 or less after 5 years.

Ranibizumab  

The drug must be supplied via relevant PAS.

One single dose intravitreal injection. The treatment should be determined by individual patient response and based on disease activity. Many patients may only need one or two injections during the first year, while some patients may need more frequent treatment, including a monthly injection.

6. Vitreomacular traction (VMT)

Vitreomacular traction (VMT) is a progressive condition with can potentially lead to sight loss. In around 10% of people, VMT resolves spontaneously.

Ocriplasmin  

The following criteria must be met:
- an epiretinal membrane not present, and
- a stage II full-thickness macular hole with a diameter of 400 micrometres or less, and/or
- the patient has severe sight problems.

One single dose intravitreal injection.

If the fellow eye needs to be treated a minimum 7 days interval is recommended in order to allow response in the first eye.

The treatment is successful in about 40% of cases. Up to 8% of patients can experience a 2 line drop in acuity in the first week which generally recovers within a further 2 weeks without intervention. Up to 7% of cases following treatment for VMT can develop new full thickness macular hole.

Repeated injections in the same eye are not recommended due to lack of evidence on safety and efficacy.
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3. CRVO
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4. CRVO
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5. CNV secondary to pathological myopia
2. NICE TA298, Ranibizumab for treating choroidal neovascularisation associated with pathological myopia, November 2013
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