Patient Information

University Hospitals Coventry and Warwickshire NHS Trust

Macular Unit

Treatment of Wet-Age Related Macular Degeneration (Wet-AMD): Lucentis versus Avastin versus Eylea

What is Avastin and how does it differ from Lucentis and Eylea and how does Eylea differ from Lucentis and Avastin?

There are several types of anti-VEGF drugs being used in eye care: ranibizumab (Lucentis), bevacizumab (Avastin) and aflibercept (Eylea). They belong to a group of treatments known as anti-vascular endothelial growth factor (anti-VEGF) therapies.

VEGF is an important component in wound healing and maintenance of small and newly formed blood vessels. The body carefully regulates the amount of VEGF.

Anything that upsets this regulatory system may lead to an increase or decrease in the release of VEGF. In certain diseases such as wet-AMD, diabetes or retinal vein occlusions, VEGF is increased in the eye causing over-production of new fragile blood vessels which may bleed and leak fluid into the retina.

How do these drugs work?

These anti-VEGF drugs inhibit the increased release of VEGF and as a result they slow down the growth of the new blood vessels and control the wet-AMD from progressing further.

NICE has approved ranibizumab (Lucentis) for treating wet AMD and has published final draft guidance recommending aflibercept (Eylea).

Both of these drugs are licensed to treat wet-AMD effectively and successfully. Lucentis and Eylea are also licensed for a variety of other eye diseases such as visual impairment from diabetic macular oedema and retinal vein occlusions.

Avastin is a drug closely related to Lucentis and has also been shown to be an effective and a cheaper alternative. However it is licensed to treat certain cancers such as colorectal and kidney cancers and **is not licensed for the treatment of AMD in any part of the UK.**

Eylea (also called VEGF Trap Eye or aflibercept) trials suggest that it is effective for longer than Lucentis and so may mean fewer injections are needed. Eylea treatment is initiated with one injection per month for three consecutive doses followed by one fixed injection every two months which means 7-8 injections in the first year. So patients might typically require fewer follow up appointments than those treated with Lucentis or Avastin.

Due to the impact of the intravitreal injections on services we are not restricted to monthly injecting; alternative approaches to maintenance have been developed. 'PRN' has fixed monitoring intervals but the patient receives an injection only if the scan shows a recurrence of fluid or haemorrhage. 'Treat and extend' has the patient receive an injection at every visit, but the gap between visits is stretched to a maximum of 12 weeks, unless there are indications that a return to more frequent treatment is required. 'Treat and extend' has been shown to be an effective approach, reducing treatment burden. Freund K, Korobelnik JF, Devenyi R, Framme C, Galic J, et al. (2015). Treat-and-extend regimens with Anti-VEGF agents in retinal diseases: A Literature Review and Consensus Recommendations. *Retina* 35(8):1489-1506.

What does unlicensed mean?

Unlicensed medicines are medicines or substances used as medicines without a UK marketing authorisation. The use of unlicensed drugs is actually very common in medicine. Doctors may use medications “off-label” (unlicensed) for other purposes if they are well-informed about the product, base its use on sound medical evidence, and maintain records of its use and effects.

Generally if an unlicensed medicine is administered to a patient the manufacturer may not have liability for any harm that ensues. The person who prescribes and dispenses or supplies the unlicensed medicine carries the liability. In the NHS environment this liability is shared with the hospital Trust that authorises the unlicensed use of the drug. This would be the case for Avastin used instead of Lucentis or Eylea for wet-AMD cases, for which NICE (National Institute of Clinical Excellence) recommends.

Unlicensed medicines are only used where their use is clearly justified and their clinical/pharmaceutical benefits are considered to outweigh the risks involved.

Drugs used for licensed indications are monitored for safety at international level via licensing regulations. Drugs used outside licensed indications, such as Avastin to treat wet-AMD or other retinal diseases, have no structured arrangements for safety monitoring other than local ones.

In December 2011, following a review of the efficacy of Avastin and Lucentis in the treatment of AMD the Royal College of Ophthalmologists recommends that the ‘NHS should urgently instruct NICE and the Medicines and Healthcare Products Regulatory Agency (MHRA) to evaluate the use of Avastin in the treatment of AMD and produce national guidelines’. This view is supported by the Macular Disease Society (MDS Digest 2012) who is also calling for a national review of the use of Avastin in ophthalmology.

How safe is it?

The only approved studies of potential side-effects of Avastin, relate to its use as a cancer treatment where the drug is used in much larger doses and is given intravenously. This cannot be compared with its use as an eye treatment where the dose is significantly smaller and is injected directly into the eye and not into a vein. In April 2011 the results of a USA clinical trial supported the use of Avastin as an effective, low cost alternative to Lucentis. A small increase in adverse side effects in the Avastin group (24% compared with 19% for Lucentis) was reported but researchers felt that this was most likely due to statistical or technical reasons and did not regard this as a reason to stop using Avastin. (CATT trial 10.1056/NEJMoa1102673 April 28 2011 at NEJM.org).

A UK study IVAN www.cteu.bris.ac.uk/trials/ivan/GeneralInfo.aspx#h1 looked at the comparative effectiveness of the two drugs Avastin and Lucentis. The preliminary results from the first year of a trial comparing the efficacy and safety of bevacizumab (Avastin) and ranibizumab (Lucentis) found there was no functional difference in the effects of both drugs and that their effects on preventing vision loss were similar.

In summary both IVAN and CATT studies have consistently shown no difference in mortality between the groups receiving different drugs, but both found a slightly higher rate of other serious adverse events in those who received Avastin. This evidence became stronger when the results were combined.

However the researchers state that the findings in relation to adverse events may not be attributed to Avastin directly, due to a number of reasons, including that events were more common in patients treated less frequently and that they arose mainly from hospitalisations for a wide variety of causes not previously associated with either drug.

A more recent study in the US found the two drugs had a similar effect on visual acuity after two years. However the study also found that patients treated with bevacizumab (Avastin) suffered a higher number of adverse events than those treated with

ranibizumab (Lucentis) but was unable to conclude if this was due to differences between the drugs. (Martin, DF et al (2012) Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration: Two-Year Results. *Ophthalmology*, Volume 119, Issue 7, July 2012, Pages 1388-1398.)

What are the potential risks?

As with any procedure involving injections there is the potential for side-effects which you need to be aware of and will be discussed with you. These include:

- Systematic exposure. Although the likelihood of systemic exposure is low, the injected drug will leak out of the eye and into your blood stream. Lucentis takes two hours for it to be cleared out of your body, whilst Avastin can take up to 21 days. If there are sufficient amounts Avastin in the blood stream this may have unknown effects.
- Avastin contains no preservatives and is pre-packed by the manufacturer in larger vials for intravenous use. Small amounts of Avastin are then drawn up by pharmacists into syringes for eye injection use under sterile conditions and sent to eye units. In theory, there may be a small risk of contamination during this process as opposed to factory pre-packed sterile Lucentis and Eylea
- Avastin may have a slightly greater risk of causing inflammation or raised pressure in the eye. However, these infrequent and unlikely sight-threatening side effects would be addressed by switching from Avastin to Lucentis during the course of treatment.
- The body may react to the larger monoclonal antibody protein contained in Avastin, by forming its own antibodies to fight against these drugs. This may be the reason why long term loss of efficacy has been observed in some patients, slightly more with Avastin (full antibody) than Lucentis/Eylea (antibody fragment).

Other known risks of the procedure for eye injections not related to the type of drug being used

Your condition may not get better or may become worse. These complications may cause decreased vision or possibly blindness. Additional procedures may be needed to treat these complications.

Possible complications and side effects of the procedure and administration of Avastin include but are not limited to:

- The possibility of a severe eye infection which can cause blindness known as Endophthalmitis
- Retinal detachment
- Cataract (clouding of the lens)
- Glaucoma (increased pressure in the eye)
- Hypotony (reduced pressure in the eye)
- Damage to the retina or the front of the eye called the cornea
- Bleeding.

Summary of the main differences between Eylea/ Lucentis/ Avastin

Eylea	**Lucentis**	**Avastin**
Licensed	Licensed	Unlicensed
Monthly injections for first three months then bimonthly follow- ups and injection	Monthly injections for first three months then monthly follow-ups and injection if required	Monthly injections for first three months then monthly follow-ups and injection if required
More injections in the first year as it is a fixed number and not individualised	Less injections in the first year as it is individualised to patients' need and is not fixed	Less injections in the first year as it is individualised to patients' need and is not fixed
Fewer follow-ups in the first year	More frequent follow-ups in the first year	More frequent follow ups in he first year

Effect lasts longer than 28 days Long term efficacy is not known yet	Effect lasts no longer than 28 days removed from the body in 2 hours Small chance of long term loss of efficacy	Effect lasts no longer than 28 days remains in the body for 21 days Slightly greater chance of long term loss of efficacy
Monitored for safety at international level via licensing regulations	Monitored for safety at international level via licensing regulations	No structured arrangements for safety monitoring other than local ones
Benefit to vision well documented by various clinical trials for wet-AMD.	Benefit to vision well documented by various clinical trials for wet-AMD, vein occlusion and diabetes.	Benefit to vision shown to be not inferior to Lucentis in a large USA clinical trial (CATT). There are no good quality direct comparison studies of Avastin versus Lucentis to asses benefit for non-wet AMD eye diseases.
Small chance of persistent raised eye pressure after an injection	Small chance of persistent raised eye pressure after an injection	Slightly higher chances of persistent raised eye pressure after an injection
In theory, small risk of stroke or heart attack. No study so far has confirmed this. There is ongoing monitoring of Eylea as part of the licensing process.	In theory, small risk of stroke or heart attack. No study so far has confirmed this. There is ongoing monitoring of Lucentis as part of the licensing process.	In theory, small risk of stroke or heart attack. Slightly higher adverse events compared with Lucentis Overall Avastin appears to be safe. You may read on the Internet of studies that have shown weak associations of Avastin for wet-AMD with stroke, heart conditions or gastrointestinal bleeding. These studies were deemed not to be conclusive enough to put patients and ophthalmologists off Avastin.

So why am I given Avastin?

You have been offered Avastin because you are not eligible for Lucentis or Eylea according to the local commissioning policy. www.coventryrugbyccg.nhs.uk/About-Us/Policies

This is due to one of the following reasons:

1. You have a sub-type of disease called RAP or polypoidal vasculopathy, which locally, is not funded for Eylea or Lucentis but is funded for Avastin.

2. You do not meet one or more of the following NICE qualifying criteria for funding of Lucentis or Eylea
    a. Visual acuity has to fall within the NICE criteria
    b. Location and size of the AMD lesion
    c. There are signs of disease progression
    d. There are no signs of permanent structural damage of the most central part of the eye

There is good evidence to show that Avastin is not inferior to Lucentis for the improvement or stabilisation of vision in wet-AMD. Eylea and Lucentis are comparable.

At present it is unclear if commissioners (who pay for the service) will allow switching from Lucentis to Eylea or vice versa according to clinical needs

Avastin is substantially cheaper than Lucentis /Eylea and its use will help ensure that NHS resources, in particular Macular Services, will be available to as many patients as possible, ultimately serving the best interests of the wider community.

The following links provide more information about the current debate concerning the use of Avastin and Lucentis:

www.rcophth.ac.uk/news.asp?itemid=647&itemTitle=RCOphth+Review+concludes+that+Avastin+and+Lucentis+are+equally+effective+in+treating+wet+AMD&section=24&sectionTitle=News

www.maculardisease.org

You may also want to request to view your local health commissioning group's (www.coventryrugbyccg.nhs.uk/About-Us/Policies) on commissioning AMD treatment.

If you have any further queries or concerns please contact the Macular Unit at Rugby St Cross Hospital Tel. 01788 663390 or 01788 663338

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